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Clinical Significance of a Panel Tests in Evaluating Central Nervous System Infections

Fang Jiang[1#], Wen Jun Yu[2#], Xiaoyang Jiao[3], Mengya Si[1] and Xuehua Wang[1*]

[1]The First Affiliated Hospital of Shantou University Medical College, Shantou 515041, China

[2]The Second Affiliated Hospital of Shantou University Medical College, Shantou 515041, China

[3]Department of Cell Biology and Genetics, Shantou University Medical College, Shantou 515041, China

[#]These authors contributed equally to this study.

[*]**Corresponding author**: Xuehua Wang, The First Affiliated Hospital of Shantou University Medical College, Shantou 515041, China

Abstract

Aim: The FilmArray ME Panel is an emerging diagnostic method for detecting multiple pathogens in cerebrospinal fluid (CSF). We evaluated the clinical significance of the FilmArray ME Panel in the diagnosis of central nervous system (CNS) infection.

Methods: CSF specimens of 130 patients with suspected CNS infection were analyzed, along with clinical and laboratory parameters.

Results: patients shared some clinical symptoms at presentation, including fever, headache, altered mental status, and focal neurologic deficits. In a total of 130 patients, pathogens were detected in 22 cases, which included eight bacterial infections, and fourteen viral infections. The predominant bacteria detected in CSF were Streptococcus pneumonia, while the most common virus was enterovirus. The FilmArray ME panel had a better coincidence rate with PCR for viral detection, but had higher sensitivity compared with conventional bacterial detection.

Conclusions: The FilmArray ME Panel provides rapid diagnosis that benefits enabling patients to be promptly treated, improving the effectiveness of treatment.

Keywords: Central nervous system infection; FilmArray ME panel; Meningitis; Encephalitis

Introduction

Central Nervous System (CNS) infections are a significant cause of mortality and morbidity throughout the world [1]. CNS infections, such as meningitis and encephalitis, can result from bacteria, viruses, fungi and parasites. Besides microorganisms, the causes of neuroinflammation include autoimmunity, trauma, degenerative processes, toxins, and malignancy. However, many patients with neuroinflammation have unknown causes [2]. In clinical practice, CNS inflammation with non-infectious causes have similar clinical features to infectious causes, with some overlapping laboratory features based on the Cerebrospinal Fluid (CSF) or blood measurement [3,4]. An incomplete understanding of the etiology of CNS infection is the main factor responsible for higher mortality and morbidity in patients with CNS infections [5,6]**.** Therefore, insight into microbial - host interactions involving in CNS infections and its relevant neurologic sequelae is instrumental in improving patient treatment and prognosis, reducing mortality, and developing new therapeutic strategies for CNS infection [1]. Many pathogens cause CNS infections. Unfortunately, the underlying pathogenes is not found in as many as 40% - 60% of patients [7]. Examination of CSF is of vital importance for the diagnosis of CNS infection. Routine CSF examinations include biochemical tests (LDH, protein, glucose, and chloride), cytologic tests, including White Blood Cell (WBC) and differential count, and CSF bacterial culture. None of the above methods can precisely and sensitively detect pathogens. Bacterial and viral meningitis account for the majority of CNS infections, and their detection in CSF includes bacterial culture, antigen detection, and chemical, and cellular analyses [8]. Culture methods provide a definitive diagnosis for bacterial infection, which requires 2 to 5 days and may be falsely negative if the bacteria are fastidious or the patient was treated with antibiotics, or the specimens were improperly processed [9]. The evaluation of patients with probable viral CNS infection is complicated for lack of unified diagnostic criteria, the number of possibilities of virus that cause such infections, and the limited number of diagnostic tools [10]. Polymerase Chain Reaction (PCR) is a fast and specific method to detect pathogens, but single probe selection is not suitable for the detection of various unknown pathogens. The California Encephalitis Project was a multitudinous study of suspected encephalitis cases (n =1570), over seven years, which was predicated on the pathogeny of encephalitis cases. However, 63% of cases had unexplained etiology in the study despite extensive attempts to identify potential causes [11]. Failure to obtain a timely diagnosis delays choosing an appropriate therapy. The mortality rate of untreated bacterial meningitis approaches 100% and, even with timely treatment, mortality and morbidity still occurs [12].

Nowadays, bacterial meningitis is one of the top 10 reasons for universal infection-related mortality. Present strategies for therapy of CNS infection are compromised by the uncertainty of microbial-host interactions [13]. Etiological specificity tests can improve the therapeutic effect and the prognosis. Compared to the conventional tests, detection focusing on microorganisms undoubtedly has a great advantage. PCR provides high sensitivity and specificity, and can reliably diagnose pathogens, especially for fastidious bacteria [14,15]. Compared with the culture and serological methods, PCR method requires a shorter time, in addition, the results of PCR are not affected by patient treatment with antibiotics. Currently, PCR is extensively used for detecting microorganisms in some tertiary hospitals. However, the disadvantage of conventional PCR techniques is also significant, since it only detects one pathogen at a time and needs to catch in batches. The time- and labor-intensiveness of PCR limits its widespread use in the diagnosis of CNS infection. In recent years, several advanced molecular diagnostic techniques show promise for rapid diagnosis, such as the GeneXpert MTB/RIF assay and loop-mediated amplification of microorganisms. However, these techniques are impractical because of the relatively

high cost and the requirement for experienced professionals. The FilmArray ME Panel is a multiplexed nucleic acid test for the simultaneous qualitative detection and identification of a considerable number of pathogens in the CSF, and has better effectiveness compared with culture and other methods [9]. The whole process of detection only takes about an hour. Compared to traditional PCR, the FilmArray ME Panel provides fast results. Therefore, the method seems to have great potential for application. As the FilmArray ME is a novel method, it has yet to find wide use in clinical specimen detection, and its clinical significance remains to be evaluated. In this study, we recruited 130 patients with suspected meningitis, their pathogens were measured by the FilmArray ME Panel, as well as the conventional CSF tests.

Materials and Methods

The study protocol was approved by the Ethics Committee of Shantou University Medical College. Informed written consents were obtained before inclusion by the patient or by their guardian.

Patients

Patients were recruited according to the following criteria: patients with fever, headache, seizure or depressed consciousness (at least one presenting symptom). Signs of cervical stiffness, alteration of consciousness, cranial nerve palsy, or plegia/paresis upon physical examination. The CSF specimen met at least one of the following criteria: 1: White Blood Cells (WBCs) ≥ 5 cells/high power field (<50% polymorphonuclear leukocytes), protein >50 mg/dL, glucose <60 mg/dL or CSF plasma glucose ratio < 0.4. Patient demographics, laboratory results, clinical characteristics, imaging, therapy, and prognoses were recorded. We acquired clinical data from the patient charts that met the conditions.

Biochemical and cytologic testing of CSF

The cytologic tests included WBC count and differential count. Biochemistry results included serum creatinine, LDH, serum or CSF glucose, protein, and chloride.

Bacterial culture for blood or CSF

Bacterial cultures for both blood and CSF were performed on every specimen enrolled. Testing used standard clinical laboratory procedures.

FilmArray ME Panel testing

The FilmArray ME Panel can simultaneously detect 14 pathogens in CSF specimens. Approximately 200 µl of the sample was subjected to FilmArray® ME Panel testing according to the manufacturer's instructions. The 14 pathogens detected in CSF were: Hemophilus influenza, Neisseria meningitides, Escherichia coli K1, Listeria monocytogenes, Streptococcus pneumonia, Streptococcus agalactiae, Enterovirus (EV), Cytomegalovirus (CMV), Herpes Simplex Virus type 1/2 (HSV-1/2), Human Herpesvirus Type 6 (HHV-6), Varicella Zoster Virus (VZV), Human Parechovirus (HPeV), and Cryptococcus neoformans/gattii.

Results

Between November 2017 to October 2018, 130 patients were enrolled in this study. Clinical and demographic data were presented in **Table 1**. The mean age of patients was 28 years. There were 82 male and 48 female patients, giving a male/female ratio of 1.74:1. The most common symptom was fever, which was found in 95% of patients. Headache was the second most common symptom, with 71 % of patients having this problem. For other symptoms, 37% of patients had vomiting, 39% of patients were apathetic, 25% of patients had nausea and

neck rigidity, 22% of patients had twitches, and 16% of patients had a disorder of consciousness. Signs of meningeal irritation presented in 11.5% of patients, and 80% of patients had fever and apathetic symptoms in the bacterial infection group. The patients with viral and fungal infections also shared the similar symptoms. There was a prominent overlap in clinical features, including fever, headache, focal neurologic deficits, and altered mental status. Twenty-one cases of patients had systemic disease, 18 patients had epilepsy, 7 patients had high blood pressure, 5 patients had heart disease, and 4 patients had diabetes. The onsite analysis showed that all samples had at least five leukocytes /μL in the CSF, indicating an inflammatory reaction within the CNS. During their hospital stay, thirty-one patients received antibiotic treatment (cephalosporins, astaxanthin, and sulbactam), and thirty-seven patients received antiviral drugs (oseltamivir and ribavirin), and 17 patients received combination antibiotic and antiviral treatment.

Table 1: Patients' general characteristics.

	Cases
Total	130
Age	
0-27	65
≥28	65
Gender	
Male	82
Female	48
Pathogen infection	
Virus	14
Bacterial (or fungi)	8
Unidentified	108
Treatment	
Antibiotic	31
Antiviral	37
Antiviral + Antibiotic	17
Meningitis type (based on the clinic)	
Suppurative meningitis	9
Viral meningitis	60
Autoimmune encephalitis	2
Tuberculous meningitis	13
Systemic diseases	
Diabetes	4
High blood pressure	7
Heart disease	5
Epilepsy	18
Clinical symptom	
Headache	71
Nausea	25
Vomiting	37
Fever	95
Apathetic	39
Sleepiness	7
Disorder of consciousness	16
twitch	22
Neck stiffness	25
Meningeal irritation	15

Cytologic and biochemical tests

The subgroup classified by bacterial, viral, and unidentified groups, and the CSF biochemistry tests were compared among the subgroups. The mean CSF glucose was the lowest in the S. pneumonia group, while the highest glucose was in patients with viral infections. Mean CSF protein was the highest for patients with bacterial infections, followed by patients with fungal infections, while protein levels varied widely in the viral group. CSF LDH level was the highest in the S. pneumonia group. The WBC count in CSF was elevated in the S. pneumonia group, while WBC counts in the viral group were lower than those in the bacterial group **Table 2**.

Table 2: Patient characteristics by type of pathogen detected using the CSF or serum testing.

	Value for pathogenic:								
	Bacterial		Viruses						Fungus
parameter	S.pneumonian=4	E.coli K1, n=1	Enterovirus, n=8	HHV-6, n=2	VZV, n=1	HSV1,	HSV2, n=1	CMV, n=1	Cryptococcus neoformans, n=3
CSF									
GLU	1.42	4.52	3.34	3.32	3.82	4.09	2.27	3.6	2.7
CL	120.78	116.9	118.82	118.65	125.5	107.2	116.8	113	113.83
Protein	1370.28	270	330.1	135.73	531	373	1207	850	489.4
LDH	708	34	28	40	-	-	-	24	29
ADA	16.5	-	2.63	7	3	7	11	3	2.33
IgG	26.27	1.5	14.4	4.81	-	-	-	14.6	9.17
IgA	5.21	<1.11	1.48	<1.11	-	-	-	2.63	2.5
IgM	1.65	<0.69	2.27	<0.69	-	-	-	<0.69	<0.69
WBC	5838.75	1	137.38	240.5	184	86	1236	160	220.67
Serum (LDH)/CSF (LDH)	1.68	8.35	6.61	4.33	-	-	-	5.92	19.04

Etiology determined in patients with CNS infection

Among the 130 patients, pathogens were detected in 22 patients by the FilmArray ME panel, which included 8 cases of bacterial infection, 14 cases of viral infection. Bacteria detected were Streptococcus pneumoniae (n = 4), Cryptococcus neoformans (n = 3), and E.coli K1 (n = 1). In the 14 cases of viral infection, the most common virus was enterovirus, which was detected in eight samples, followed by 2 cases of human herpesvirus type 6 (HHV-6), and the remaining viruses detected were varicella-zoster virus (1 case), cytomegalovirus (1 case), herpes simplex virus (HSV) (1 case) type 1 (HSV-1) (1 case), and 2 cases of HSV-2.

Comparison the bacterial cultures and FilmArray ME panel

Eight patients were found to have bacterial infection by the FilmArray ME Panel, among them, 4 cases were confirmed by the CSF bacterial cultures. Besides CSF culture, five patients were positive in the blood culture, thirteen cases of patients were culture positive in sputum, and seven cases of patients were detected bacterial infection in other types of specimens **(Table 3)**. The predominant bacterium in CSF was Streptococcus pneumonia (18.2%), followed by Escherichia coli (4.5%). The highest coincidence of the two methods found in Cryptococcus neoformans.

Table 3: Comparison of bacterial (or fungi) cultures and FilmArray RP.

Positive	FilmArray	Bacterial culture			
		CSF	Blood	Sputum	Others
Streptococcus pneumoniae	4	0	1	0	0
Cryptococcus neoformans	3	2	1	0	0
E.coli K1	1	0	0	0	0
Streptococcus agalactiae	0	1	2	0	0
Common bacterium	0	1	0	0	0
Staphylococcus aureus	0	0	1	0	0
Staphylococcus aureus	0	0	0	4	1
Klebsiella pneumoniae	0	0	0	2	0
Acinetobacter baumannii	0	0	0	2	0
ECO-ESBLs	0	0	0	1	0
Haemophilus influenzae	0	0	0	1	0
Moraxella	0	0	0	1	0
Stenotrophomonas maltophilia	0	0	0	1	0
Enterobacter cloacae	0	0	0	1	0
Enterococcus faecium	0	0	0	0	2
Mycoplasma pneumoniae	0	0	0	0	1
Candida tropicalis	0	0	0	0	1
Candida albicans	0	0	0	0	1
Staphylococcus haemolyticus	0	0	0	0	1

Discussion

Prompt treatment of infectious meningitis and encephalitis are vital to minimize morbidity and mortality **[9]**. However, the etiology behind CNS infections is quite complicated, and pathogens are still not found in up to 70% of cases. Therefore, current curative treatment for CNS infections is restricted because of incomplete knowledge of the microbial-host interactions **[7,13].** In the United States, 80% of CNS infections are induced by bacteria, including Streptococcus pneumonia, Streptococcus agalactiae, Neisseria meningitides, Haemophilus influenzae, Escherichia coli (especially the K1 serotype), and Listeria monocytogenes **[9]**. Streptococcus pneumonia was the main species detected in our patients with bacterial meningitis. Currently, bacterial culture

of the CSF is still recognized as the gold standard for the diagnosis of bacterial meningitis [16,17]. However, bacterial culture requires much more time to diagnosis, and the time delay may have fatal ramifications for patients or result in needless application of broad-spectrum antibiotics and delay of effective treatment. In this study, 31 cases of patients were treated empirically, but the therapeutic efficacy varied. CSF pleocytosis is a sensitive marker of inflammation. However, some studies have confirmed that patients with bacterial meningitis may have normal WBC counts. In our study, patients infected with S. pneumonia had much higher WBC counts than patients infected with E.coli K1. WBCs in CSF differed between bacterial infection and viral infection, and the differential WBC count, especially the lymphocyte ratio, as well as the consistency of protein and glucose, are useful in the differential diagnosis of CNS infection. However, the specificity and sensitivity of these tests are low. In this study, only 4 cases of suspected patients had bacteria detected by culture, whereas in 8 cases bacteria could be detected by The FilmArray ME, a detection rate twice that of bacterial culture. Four percents of patients had a positive blood culture, 10% patients were sputum-positive who were negative in both the FilmArray ME Panel and culture methods. Whether the patient's meningeal irritation is part of a systemic infection remains to be determined. Previous large-scale study on bacterial meningitis in pediatric patients showed that only 7% of cases had positive blood cultures [18]. Viruses are the primary cause of aseptic meningitis. The main causes of viral meningitis are enteroviruses [19-21], which have been related to outbreaks of CNS infections worldwide [22]. However, the etiology of viral encephalitis varies from one region to another. HSV is the main pathogen of viral encephalitis in many countries, such as England, the USA, France, and Spain [21,23,24]. Enterovirus is the major pathogen inducing viral encephalitis in China [19]. In our study, more than half of viral meningitis infected by enterovirus, and those patients presented multifarious clinical syndromes, including aseptic meningitis, and acute flaccid paralysis/myelitis. In a state of unknown etiology, epidemiology and clinical symptoms may provide some diagnostic clues. In clinic, one of the challenges in the diagnosis of CNS disease is the coincide in the clinical presentation of a considerable variety of diseases [25]. Rapidly distinguishing CNS infections from other brain and spinal cord disorders is critical for adequate treatment, which ultimately determines the patient's prognosis. The FilmArray ME Panel can detect a broad range of pathogens in CSF, representing a significant paradigm shift of performance from culture to molecular reference methods. In this study, enterovirus-positive specimens were re-examined by PCR, and the coincidence rate was 100%, whereas for bacterial detection, the FilmArray ME Panel had twice the detection rate of bacterial culture. The high incidence of prior antibiotic treatment before intervention may have reduced the detection rate of pathogenic bacteria [26]. Our results show that the FilmArray ME Panel has significant advantages compared to bacterial culture. In a previous study, about 60% of patients obtained a definite diagnosis [4] and mandated empiric antimicrobial therapy. Frequent use of broad-spectrum antibiotics will result in multidrug resistance [27,28]. Empiric therapy for patients with bacterial meningitis is prevalent in areas with penicillin-resistant and third-generation cephalosporin-resistant S. pneumonia [13]. Rapid tests for both bacterial and viral pathogens will be considerably useful for young infants, and may potentially provide more targeted therapy. Because of its large number of advantages, including close-to-patient, rapid detection of a broad range of infectious agents associated with CNS infections [9], the FilmArray ME Panel has a wide range of prospective applications in clinical practice.

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