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Use of the FilmArray® Meningitis/Encephalitis panel to detect pathogenic microorganisms in cerebrospinal fluid specimens: a single-center retrospective study

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Abstract

Objective: Meningitis and encephalitis are neurological emergencies requiring rapid diagnosis and treatment. The performance of the FilmArray® Meningitis/Encephalitis (ME) panel, a multiplex polymerase chain reaction test, and conventional methods for diagnosing meningitis and encephalitis was compared.

Methods: This retrospective study assessed 20 patients diagnosed with meningitis or encephalitis according to clinical symptoms and laboratory examination findings between January 2018 and December 2019. The results of the FilmArray® ME panel were compared with those of conventional methods.

Results: Pathogens were identified in 11 (55%) patients using the FilmArray® ME panel and in nine (45%) patients using conventional methods. The test identified herpes simplex virus type 1 in two patients, herpes simplex virus type 2 in one, varicella-zoster virus in four, *Streptococcus pneumoniae* in three, and *Cryptococcus neoformans* in one. Furthermore, additional pathogens were detected (n = 1, *S. pneumoniae* and n = 1, varicella-zoster virus). The median times to pathogen identification were 2 hours using the FilmArray® ME panel and 96 hours with conventional methods.

Conclusions: The sensitivity of the FilmArray® ME panel for rapidly detecting the most common pathogens was similar to that of conventional methods. Hence, this method could decrease the time to definitive diagnosis and treatment initiation.

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Introduction

Meningitis and encephalitis are neurological emergencies that require prompt diagnosis and treatment.[1] Meningitis is an inflammation or infection of the meninges that typically causes signs and symptoms such as fever, headache, and stiff neck. Meanwhile, encephalitis is an inflammation or infection of brain tissues and is characterized by altered consciousness, seizures, or focal neurological signs. The conventional methods for the diagnosis of meningitis and encephalitis include Gram staining of the cerebrospinal fluid (CSF), CSF bacterial culture, bacterial and fungal antigen tests, viral polymerase chain reaction (PCR), and blood cultures.[2] The prompt initiation of empirical antimicrobial treatment is recommended.[1] If the diagnosis is accurate, appropriate empirical therapy targeting the causative organism can be provided. Although this treatment strategy is beneficial, rapid and accurate diagnosis and early specific treatment are associated with a more favorable outcome.

The FilmArray® Meningitis/Encephalitis (ME) panel (BioFire Diagnostics, LLC, Salt Lake City, UT, USA) is a novel molecular multiplex PCR assay that can detect the 14 most common causative pathogens of central nervous system infections.[3,4] The current study aimed to compare the performance of the FilmArray® ME panel with that of conventional methods for diagnosing meningitis and encephalitis.

Methods

This single-center, retrospective, observational study included patients diagnosed with meningitis or encephalitis according to clinical symptoms and laboratory examination findings at the Division of Neurology of Nihon University School of Medicine between January 2018 and December 2019. Our division cares for adult patients, not children (<16 years old). Participants with preserved CSF samples that were assessed using the FilmArray® ME panel were included in the analysis. The medical records of all patients were reviewed. Data on clinical presentation, laboratory data including CSF analysis results, and discharge diagnoses were obtained. The participants were diagnosed with meningitis or encephalitis based on clinical findings including neurological signs and brain imaging results.

Assays were performed with the FilmArray® ME panel, which can identify six bacteria (*Escherichia coli K1*, *Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactiae,* and *Streptococcus pneumoniae*), seven viruses (herpes simplex virus types 1 [HSV-1] and 2 [HSV-2], varicella-zoster virus [VZV], cytomegalovirus, human herpesvirus 6, human parechovirus, and enterovirus), and one yeast group (*C. neoformans/gattii*) (Table 1). The CSF specimens (approximately 200 μL) were subjected to a FilmArray® ME panel.[5] Bacterial meningitis was diagnosed via Gram staining of the CSF and/or CSF bacterial culture, which are conventional methods. Viral meningitis or encephalitis was identified using a commercial HSV/VZV quantitative real-time PCR (qRT-PCR) assay (SRL, Inc., Tokyo), and cryptococcal

Table 1. Detection targets of the FilmArray® Meningitis/Encephalitis panel.

Bacteria	Viruses	Yeast group
Escherichia coli K1	Herpes simplex virus type 1	*Cryptococcus neoformans/gattii*
Haemophilus influenzae	Herpes simplex virus type 2	
Listeria monocytogenes	Varicella-zoster virus	
Neisseria meningitidis	Cytomegalovirus	
Streptococcus agalactiae	Human herpesvirus 6	
Streptococcus pneumoniae	Human parechovirus	
	Enterovirus	

meningitis was diagnosed based on positive culture results from blood and/or CSF samples or a positive cryptococcal antigen test finding. The results of the FilmArray® ME panel and the conventional methods were compared. The time to obtain a clinical diagnosis on the basis of the results of each test was compared using the Mann–Whitney U test, and a P value of <0.05 was considered significant.

This study was approved by the ethics committee of Nihon University School of Medicine (RK-201110-01) and was performed in accordance with the Declaration of Helsinki and the STROBE guidelines.[6] The study was conducted using opt-out consent of patients.

Results

During the study period, 34 patients diagnosed with meningitis or encephalitis were admitted to our department. In total, 20 patients with preserved CSF samples who were tested using the FilmArray® ME panel were included in the analysis. The remaining 14 patients without CSF samples were not included. Table 2 shows the demographic characteristics and the performance of the FilmArray® ME panel in each patient. The median age of the patients was 39 (range: 23–85) years, and 13 (65%) were women. The final clinical diagnoses were aseptic meningitis in eight patients, bacterial meningitis in four, VZV meningitis in four, HSV meningitis in one, HSV encephalitis in two, and cryptococcal meningitis in one. The pathogens were identified in 11 (55%) patients using the FilmArray® ME panel and in nine (45%) patients with conventional methods. Similar to the conventional methods, the FilmArray® ME panel identified HSV-1 in two patients, HSV-2 in one, VZV in three, *S. pneumoniae* in two, and *C. neoformans* in one. Furthermore, it detected additional pathogens (*S. pneumoniae*, patient 4 and VZV, patient 17). However, the conventional methods did not detect these pathogens. The FilmArray® ME panel yielded negative results in nine (45%) of 20 patients, and similar results were obtained using the conventional methods. As shown in Table 2, the median times to diagnosis after pathogen confirmation were 2 hours with the FilmArray® ME Panel and 96 hours with the conventional methods (P value <0.001) (Table 1). The results of the commercial HSV/VZV qRT-PCR assay could be obtained after 72 to 96 hours. The time required for multiplex PCR using the FilmArray® ME panel was approximately 1 hour. However, the whole process including the preparation of preserved samples required 2 hours.

The causative organism of bacterial meningitis could not be identified using either the FilmArray® ME panel or conventional methods in a 63-year-old patient with cancer who had pyelonephritis and sepsis

Table 2. Demographic characteristics of the participants and results of the FilmArray® ME panel and conventional methods.

			FilmArray® ME Panel		Conventional methods	
Case	Age, sex	Clinical diagnosis	Pathogen	TtoD	Pathogen	TtoD
1	38, M	VZV meningitis	VZV	2 h	VZV DNA, 2.6×10^3 copies/mL	96 h
2	28, F	Aseptic meningitis	Negative	2 h	Negative	72 h
3	24, F	Aseptic meningitis	Negative	2.5 h	Negative	72 h
4	85, F	VZV meningitis	VZV	2 h	Negative	48 h
5	67, M	HSV encephalitis	HSV-1	2 h	HSV DNA, 9.2×10^4 copies/mL	96 h
6	39, F	Aseptic meningitis	Negative	2 h	Negative	96 h
7	63, M	Bacterial meningitis	Negative	2.5 h	Negative (culture, Ag)	96 h
8	37, F	Aseptic meningitis	Negative	2 h	Negative	120 h
9	69, F	Cryptococcal meningitis	*C. neoformans*	2 h	*C. neoformans* (culture)	24 h
10	40, M	Aseptic meningitis	Negative	2 h	Negative	96 h
11	43, F	Bacterial meningitis	*S. pneumoniae*	2 h	*S. pneumoniae* (culture, Ag)	24 h
12	38, F	Aseptic meningitis	Negative	2 h	Negative	72 h
13	30, F	Aseptic meningitis	Negative	2 h	Negative	120 h
14	78, F	VZV meningitis	VZV	2 h	VZV DNA, 1.2×10^3 copies/mL	96 h
15	64, M	Bacterial meningitis	*S. pneumoniae*	2 h	*S. pneumoniae* (culture)	120 h
16	23, F	VZV meningitis	VZV	2.5 h	VZV DNA, 5.1×10^3 copies/mL	72 h
17	35, M	Bacterial meningitis	*S. pneumoniae*	2 h	Negative	144 h
18	27, M	Aseptic meningitis	Negative	2 h	Negative	96 h
19	74, F	HSV encephalitis	HSV-1	2 h	HSV DNA, 2.1×10^3 copies/mL	96 h
20	38, F	HSV meningitis	HSV-2	2 h	HSV DNA, 1.5×10^4 copies/mL	96 h

TtoD: time to diagnosis, HSV-1: herpes simplex virus type 1, HSV-2: herpes simplex virus type 2, VZV: varicella-zoster virus, *S. pneumoniae*: *Streptococcus pneumoniae*, *C. neoformans*: *Cryptococcus neoformans*, Ag: antigen test, ME: meningitis/encephalitis, M: male, F: female.

(case 7). However, *Enterococcus* spp. was detected by blood culture. The CSF assessment results were negative. Eventually, the patient recovered with ceftriaxone treatment. On the basis of the findings, a diagnosis of *Enterococcus* spp.-related bacterial meningitis was established.

We compared the FilmArray® ME panel and commercial qRT-PCR results using longitudinally preserved CSF specimens collected from two patients with herpes simplex encephalitis. As shown in Table 3, in both cases, the FilmArray® ME panel and commercial qRT-PCR were positive for HSV DNA in the initial specimens and negative in the final specimens. In case 5, the Day 16 CSF specimen was positive for HSV DNA (with 3.4×10^2 copies/mL) on qRT-PCR. Meanwhile, the FilmArray® ME panel had negative results, which could be attributed to the initiation of antiviral therapy.

Discussion

The current study aimed to compare the clinical efficacy of the FilmArray® ME

Table 3. Comparison of viral assays that used longitudinal CSF specimens collected from patients with herpes simplex encephalitis.

Case	Age, sex	Date of assay	Commercial qRT-PCR (/mL)	FilmArray® ME Panel
5	67, M	Day 1	9.2×10^4 copies	HSV-1-positive
		Day 16	3.4×10^2 copies	Negative
		Day 23	$<1.0 \times 10^2$ copies	Negative
19	74, F	Day 1	2.1×10^3 copies	HSV-1-positive
		Day 17	$<1.0 \times 10^2$ copies	Negative

qRT-PCR: quantitative real-time polymerase chain reaction, HSV-1: herpes simplex virus type 1, CSF: cerebrospinal fluid, ME: meningitis/encephalitis, M: male, F: female.

panel with that of conventional methods for diagnosing meningitis and encephalitis. The FilmArray® ME panel can rapidly detect some of the most common causative pathogens of meningitis and encephalitis. Although it is a qualitative test, its sensitivity is similar to or greater than that of conventional methods.

Laboratory testing is essential to obtain a definitive diagnosis of meningitis and encephalitis. Conventional methods have advantages and disadvantages. Gram staining of the CSF can facilitate prompt diagnosis and has a high diagnostic sensitivity for specific organisms.[2] However, CSF culture and PCR are the gold standard diagnostic methods for bacterial meningitis and viral encephalitis, respectively.[7] However, the results of these tests can only be obtained several days after specimen collection. Therefore, conventional methods should be used with caution, and empirical antimicrobials must be administered promptly.[1] The FilmArray® ME Panel can provide rapid results. Hence, early diagnosis of meningitis and encephalitis can be obtained, which leads to the prompt initiation of definitive therapy, thereby improving the outcome.

In the current study, the time to diagnosis with the FilmArray® ME panel, including the entire process, was 2 hours. The FilmArray® ME panel is a qualitative test. However, its sensitivity was similar to or greater than that of conventional methods. Moreover, it detected additional pathogens (n = 1, *S. pneumoniae* and n = 1, VZV infection), and the conventional methods did not detect these pathogens. Antiviral agents and antibiotics had been administered to these patients before CSF collection. Thus, the conventional methods could not always identify the causative agents. Meningitis and encephalitis are caused by different bacteria, viruses, and fungi. Therefore, the most important advantage of the FilmArray® ME panel is that it can detect and identify the 14 most common pathogens even with concurrent treatment.[8,9] Moreover, the performance of this method may not be affected by treatment administered before testing.

Several studies evaluated the efficacy of the FilmArray® ME panel and found that this multiplex PCR test was more sensitive than conventional methods.[8,10] Rapid diagnosis using the FilmArray® ME panel was associated with a shorter hospitalization duration and more effective antibiotic treatment.[11] In addition to decreasing the time to definitive diagnosis and treatment initiation, this test method decreased the cost of healthcare because unnecessary antimicrobials were not administered.[12,13] Thus, the FilmArray® ME panel can improve clinical outcomes by decreasing the time to definitive diagnosis and the length of antimicrobial treatment and hospitalization.[14]

The FilmArray® ME panel yielded several positive results. However, because of

reports of false-positive and false-negative results, concerns exist about the application of this method. A meta-analysis showed high sensitivity and specificity of the FilmArray® ME panel across 14 pathogens, at 90% and 97%, respectively.[9] However, this panel could yield false-positive and false-negative results. The false-positive rate of the FilmArray® ME panel was 4% for *S. pneumoniae and S. agalactiae*, and its false-negative rate was 1.5% for HSV-1/2, Enterovirus, and *C. neoformans/gattii*.[3,9,15] If there is a high index of clinical suspicion for herpes simplex encephalitis despite a negative result on the FilmArray® ME panel, additional testing using qRT-PCR should be performed.[9] In the case of cryptococcal meningitis, the FilmArray® ME panel should not be used for follow-up after antifungal therapy, in contrast to its use for cryptococcal antigens.[9,15] In this study, a similar pattern was observed for a clinical case of herpes simplex encephalitis. The minimum sensitivity of qRT-PCR is 1.0×10^2 copies/mL, and the minimum sensitivities of the FilmArray® ME panel are 1.51×10^3 copies/mL for HSV-1 and 1.29×10^3 copies/mL for HSV-2.[5] The clinical guidelines recommend the confirmation of a negative HSV DNA result before the discontinuation of acyclovir in herpes simplex encephalitis.[16] The FilmArray® ME panel is useful for the initial diagnosis of herpes simplex encephalitis. However, qRT-PCR is more suitable for monitoring after the initiation of antiviral therapy.[17]

In addition, the FilmArray® ME panel cannot identify some bacteria including *Mycobacterium tuberculosis* and viruses. In this study, one patient with negative results on the FilmArray® ME panel had bacterial meningitis in which *Enterococcus* spp. was the suspected causative organism. The incidence of infections caused by *Staphylococcus* sp, *Pseudomonas aeruginosa*, Klebsiella sp, and *Enterococcus* sp is increasing in patients with chronic wasting disease or those who have undergone invasive procedures.[18] The FilmArray® ME panel does not include these organisms as test targets. In cases of nosocomial infections or infections after neurosurgery, PCR only detects <20% of all causative organisms of bacterial meningitis.[19–21] Hence, in these conditions, the efficacy of the FilmArray® ME panel could also be low.[22]

The current study had several limitations. First, it was performed at a single center. Hence, our results may not be representative of those at other institutions. Second, the sample size was small. Third, because the study was retrospective in nature, some data could have been missing. We focused on patients who were highly suspected of having meningitis or encephalitis. Therefore, all patients were treated with anti-infection therapy. The negative results obtained using the FilmArray® ME panel in nine patients were confirmed using conventional methods. However, causes other than infections could not be ruled out.

In conclusion, the FilmArray® ME panel can rapidly detect and identify the common causative pathogens of meningitis and encephalitis. It has a high specificity, similar to that of conventional methods. Furthermore, it can obtain faster results, thereby decreasing the time to definitive diagnosis and treatment initiation. However, conventional methods and information about the white blood cell count in the CSF or any pretreatment with antibiotics are still essential in diagnosing meningitis and encephalitis. Clinicians should start empiric antimicrobial and antiviral therapy based on the FilmArray® ME panel results, clinical presentation, and CSF biochemical pattern.

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Author Contributions

M.H. contributed to the experimental design, manuscript writing, and data analysis. M.I. contributed to the data analysis and manuscript revision. H.N. contributed to the data analysis, manuscript revision, and study supervision. All authors approved the final version of the manuscript.

Declaration of conflicting interests

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