Evaluation of the FilmArray Meningitis/Encephalitis Panel for Detection of Pathogenic Microorganisms in Cerebrospinal Fluid Specimens

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Research Article

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Abstract

Background: Infectious meningitis and encephalitis are neurological emergencies that necessitate rapid diagnosis and treatment. Prompt initiation of empirical antimicrobials is common practice in suspected cases. However, swifter definite diagnosis and an earlier start of definitive treatment may improve outcomes. We compared the BioFire FilmArray Meningitis/Encephalitis (ME) Panel, a multiplex polymerase chain reaction test, with conventional standard methods of diagnosing infectious meningitis and encephalitis.

Subjects and methods: We retrospectively studied 20 patients in whom meningitis or encephalitis was diagnosed according to clinical symptoms and laboratory findings between January 2018 and December 2019 at our institution. The results of pathogen diagnosis by the FilmArray ME Panel were compared with those of conventional methods.

Results: The median age of the patients was 39 years (range, 23 to 85 years), and 13 (65%) were women. The FilmArray ME Panel identified the following pathogens: herpes simplex virus (HSV)-1 in two patients, HSV-2 in one, varicella-zoster virus (VZV) in four, *Streptococcus pneumoniae* in three, and *Cryptococcus neoformans* in one. This test detected additional pathogens in one patient with *S. pneumoniae* and in one with VZV, whereas the conventional methods did not. The median time to pathogen identification was 2 h with the FilmArray ME Panel but 4 days with conventional methods.

Conclusion: Our findings suggest that the FilmArray ME Panel can detect and identify the most common pathogens faster and more sensitively than can conventional methods. This new method would thus help improve clinical outcomes through definitive diagnosis and treatment.

Introduction

Infectious meningitis and encephalitis are neurological emergencies that necessitate prompt diagnosis and treatment [1]. Conventional standard methods for the diagnosis of meningitis and encephalitis include lumbar puncture for cerebrospinal fluid (CSF) Gram stain, CSF bacterial culture, testing for bacterial and fungal antigens, and viral polymerase chain reaction (PCR), as well as blood cultures [2]. Prompt initiation of empirical antimicrobial treatment is recommended [1]. If the diagnosis is established, the efficacy of treatment could be increased by the provision of empirical therapy targeting the causative organism. Although this medical treatment strategy is beneficial, more rapid definite diagnosis and an earlier start of specific treatment can result in a more favorable outcome.

The FilmArray Meningitis/Encephalitis (ME) Panel (BioFire Diagnostics, LLC, Salt Lake City, UT, USA) is new molecular method of multiplex polymerase chain reaction (PCR) testing that can detect the 14 most common pathogens in central nervous system infections [3, 4]. In this study, we compared the performance of the FilmArray ME Panel with that of conventional methods for diagnosing infectious meningitis and encephalitis.

Patients And Methods

This study was a single-center, retrospective, observational study. Twenty patients in whom meningitis or encephalitis was diagnosed according to clinical symptoms and laboratory findings between January 2018 and December 2019 were enrolled. We analyzed laboratory data from CSF specimens sampled by lumbar puncture and performed assays with the FilmArray ME Panel. The FilmArray ME Panel 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 (*Cryptococcus neoformans/gattii*). The CSF specimens (total, approximately 200 µL) were subjected to FilmArray ME Panel testing and conventional testing (CSF Gram stain, CSF bacterial culture, tests for bacterial and fungal antigens, and viral PCR), and the results were compared.

This study was approved by the ethics committee of the Nihon University School of Medicine.

Results

The demographic characteristics and all test results for each patient are listed in Table 1. The median age of the patients was 39 years (range, 23 to 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 by the FilmArray ME Panel in 11 patients (55%) and by conventional methods in 9 (45%). The FilmArray ME Panel identified HSV-1 in two patients, HSV-2 in one, VZV in four, *S. pneumoniae* in three, and *C. neoformans* in one. This test also detected additional pathogens in one case of *S. pneumoniae* infection (patient 4) and one case of VZV infection (patient 17), whereas the conventional methods did not. The FilmArray ME Panel yielded negative results (none falsely negative) for 9 (45%) of the 20 patients, and all these cases were also confirmed negative by conventional methods. The median time to pathogen identification was 2 h with the FilmArray ME Panel and 4 days with the conventional methods.

Table 1
Patient demographics and results of the FilmArray Meningitis/Encephalitis Panel and conventional standard testing

Case	Age, sex	Clinical diagnosis	FilmArray Meningitis/Encephalitis Panel		Conventional standard testing	
			Pathogen diagnosis	Time to diagnosis	Pathogen diagnosis	Time to diagnosis
1	38, M	VZV meningitis	VZV	2 h	VZV DNA, 2.6×10^3 copies/mL	4 days
2	28, F	Aseptic meningitis	Negative	2 h	Negative	3 days
3	24, F	Aseptic meningitis	Negative	2.5 h	Negative	3 days
4	85, F	VZV meningitis	VZV	2 h	Negative	2 days
5	67, M	HSV encephalitis	HSV-1	2 h	HSV DNA, 9.2×10^4 copies/mL	4 days
6	39, F	Aseptic meningitis	Negative	2 h	Negative	4 days
7	63, M	Bacterial meningitis	Negative	2.5 h	Negative (culture, Ag)	4 days
8	37, F	Aseptic meningitis	Negative	2 h	Negative	5 days
9	69, F	Cryptococcal meningitis	<i>C. neoformans</i>	2 h	<i>C. neoformans</i> (culture)	1 days
10	40, M	Aseptic meningitis	Negative	2 h	Negative	4 days
11	43, F	Bacterial meningitis	<i>S. pneumoniae</i>	2 h	<i>S. pneumoniae</i> (culture, Ag)	1 days
12	38, F	Aseptic meningitis	Negative	2 h	Negative	3 days
13	30, F	Aseptic meningitis	Negative	2 h	Negative	5 days
14	78, F	VZV meningitis	VZV	2 h	VZV DNA, 1.2×10^3 copies/mL	4 days
15	64, M	Bacterial meningitis	<i>S. pneumoniae</i>	2 h	<i>S. pneumoniae</i> (culture)	5 days
16	23, F	VZV meningitis	VZV	2.5 h	VZV DNA, 5.1×10^3 copies/mL	3 days
17	35, M	Bacterial meningitis	<i>S. pneumoniae</i>	2 h	Negative	6 days
18	27, M	Aseptic meningitis	Negative	2 h	Negative	4 days
19	74, F	HSV encephalitis	HSV-1	2 h	HSV DNA, 2.1×10^3 copies/mL	4 days
20	38, F	HSV meningitis	HSV-2	2 h	HSV DNA, 1.5×10^4 copies/mL	4 days
<i>HSV-1</i> herpes simplex virus type 1, <i>HSV-2</i> herpes simplex virus type 2, <i>VZV</i> varicella-zoster virus, <i>S. pneumoniae</i> <i>Streptococcus pneumoniae</i> , <i>C. neoformans</i> <i>Cryptococcus neoformans</i> , Ag antigen test.						

Discussion

The FilmArray ME Panel rapidly detected some of the most common pathogens causing meningitis and encephalitis. Although it is a qualitative test, it is more sensitive than the conventional methods.

Laboratory testing is essential for the definitive diagnosis of infectious meningitis and encephalitis. The conventional methods have advantages and disadvantages. Although CSF Gram stain enables prompt diagnosis, diagnostic sensitivity depends on the organisms [2]. CSF culture for bacterial meningitis and PCR for viral encephalitis are considered the “gold standard” methods for diagnosis [5]; however, final results of these testing are often not available for several days after specimen collection. Therefore, these conventional methods should be used with caution, and empirical antimicrobials must be administered promptly [1]. Because of the rapidity of the FilmArray ME Panel for diagnosing infectious meningitis and encephalitis, it enables early initiation of definitive therapy and will contribute to better outcomes in patients with those diseases.

The FilmArray ME Panel has higher sensitivity than do the conventional methods [6]. It detected additional pathogens in two patients (one with *S. pneumoniae* infection and one with VZV infection), whereas the conventional methods did not. Because antiviral agents and antibiotics had been administered to these patients before CSF collection, the conventional methods could not always identify the causes. Meningitis and encephalitis are caused by various bacteria, viruses, and fungi; therefore, the great advantage of the FilmArray ME Panel is that it can detect and identify the 14 most common pathogens simultaneously with treatment. Moreover, treatment that is started before pathogen testing does not affect the performance of this test.

Rapid diagnosis by the FilmArray ME Panel was associated with shorter hospitalization and more effective choices of antibiotics [7]. In addition to shortening the time to definitive diagnosis and treatment, this test also helped decrease the cost of healthcare because unnecessary antimicrobials were not administered [8, 9]. Thus the FilmArray ME Panel would help improve clinical outcomes by shortening the time to definitive diagnosis and enabling shorter antimicrobial treatment and shorter hospitalization [10].

This study had several limitations. First, it was a single-facility study, and so our results may not be representative of other institutions. Second, the sample size was small. Third, because the study was retrospective, data might have been missing. We focused on patients in whom infectious meningitis and encephalitis were highly suspected; therefore, the treatment of all patients (with anti-infective therapy) was the same. The negative results of the FilmArray ME Panel for nine patients were all confirmed by conventional methods. However, causes other than infections could not be excluded.

Conclusions

The FilmArray ME Panel can rapidly detect and identify common pathogens that cause meningitis and encephalitis. It is more sensitive than conventional methods, and it provides results faster, thereby shortening the time to definitive diagnosis and initiation of treatment. The FilmArray ME Panel would thus help improve clinical outcomes, along with shortening hospitalization and enabling better choices of antibiotics.

Declarations

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Ethics approval and consent to participate:

This study was approved by the ethics committee of the Nihon University School of Medicine and followed the principles outlined in the Declaration of Helsinki for all human experimental investigations.

Conflict of interest:

The research was funded by bioMérieux Japan for reagents and a device of the FilmArray Meningitis/Encephalitis test.

Author's contributions:

M.H.: experimental design, manuscript writing, and data analysis. M.I.: data analysis and manuscript revision. H.N.: data analysis, manuscript revision, and study supervision.

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References

1. BrouwerMC, van de BeekD (2017) Management of bacterial central nervous system infections. *Handb Clin Neuro* 140:349–364. <https://doi.org/10.1016/B978-0-444-63600-3.00019-2>.
2. BrouwerMC, TunkelAR, van de BeekD (2010) Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. *Clin Microbiol Rev* 23(3):467–492. <https://doi.org/10.1128/CMR.00070-09>
3. LeberAL, EverhartK, Balada-LlasatJMetal (2016) Multicenter evaluation of BioFire FilmArray meningitis/encephalitis panel for detection of bacteria, viruses, and yeast in cerebrospinal fluid specimens. *J Clin Microbiol* 54(9):2251–2261. <https://doi.org/10.1128/JCM.00730-16>
4. PantellRH, RobertsKB, AdamsWG (2021) Evaluation and management of well-appearing febrile infants 8 to 60 days old. *Pediatrics* 148(2):e2021052228. <https://doi.org/10.1542/peds.2021-052228>
5. NigrovicLE, MalleyR, MaciasCGetal (2008) Effect of antibiotic pretreatment on cerebrospinal fluid profiles of children with bacterial meningitis. *Pediatrics* 122(4):726–730. <https://doi.org/10.1542/peds.2007-3275>
6. BoudetA, PantelA, CarlesMJetal (2019) A review of a 13-month period of FilmArray Meningitis/Encephalitis panel implementation as a first-line diagnosis tool at a university hospital. *PLoS One* 14(10):e0223887. <https://doi.org/10.1371/journal.pone.0223887>
7. NabowerAM, MillerS, BiewenBetal (2019) Association of the FilmArray meningitis/encephalitis panel with clinical management. *Hosp Pediatr* 2019;9(10):763–769. <https://doi.org/10.1542/hpeds.2019-0064>
8. SoucekDK, DumkowLE, VanLangenKM, JamesonAP (2019) Cost justification of the BioFire FilmArray meningitis/encephalitis panel versus standard of care for diagnosing meningitis in a community hospital. *J Pharm Pract* 32(1):36–40. <https://doi.org/10.1177/0897190017737697>
9. HagenA, EichingerA, Meyer-BuehnerM, SchoberT, HuebnerJ (2020) Comparison of antibiotic and acyclovir usage before and after the implementation of an on-site FilmArray meningitis/encephalitis panel in an academic tertiary pediatric hospital: a retrospective observational study. *BMC Pediatr* 20(1):56. <https://doi.org/10.1186/s12887-020-1944-2>

10. O'Brien MP, Francis JR, Marr IM, Baird RW (2018) Impact of cerebrospinal fluid multiplex assay on diagnosis and outcomes of central nervous system infections in children: a before and after cohort study. *Pediatr Infect Dis J* 37(9):868–871. <https://doi.org/10.1097/INF.0000000000001936>