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Brief communication

FilmArray Meningitis/Encephalitis (ME) panel in the diagnosis of bacterial meningitis

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ABSTRACT

The precise diagnosis of bacterial meningitis is essential. Cytological and biochemical examination of cerebrospinal fluid (CSF) are not specific. Conventional methods for bacterial meningitis lack sensitivity or take too long for a final result. Therefore, other methods for rapid and accurate diagnosis of central nervous system infections are required. FilmArray meningitis/encephalitis (ME) panel is a PCR multiplex for simultaneous and rapid identification of 14 pathogens, including 6 bacteria, 7 viruses, and Cryptococcus. We evaluated 436 CSF samples submitted to FilmArray ME Panel. Among them, 25 cases were positive for bacteria, being Streptococcus pneumonia the most frequent (48 %). Among positive cases for bacteria, 60 % were positive only with FilmArray. All the bacterial meningitis cases in which the only positive test was FilmArray had CSF findings suggestive of bacterial meningitis, including neutrophilic pleocytosis, increased CSF protein and lactate, and decreased CSF glucose. These findings suggest that FilmArray may increase the diagnostic sensitivity for bacterial meningitis.

Bacterial meningitis infections are potentially fatal central nervous system (CNS) diseases.[1] The empiric management of patients with bacterial meningitis is frequently carried out without a precise definition of the etiological agent since identification of the causative microorganism is often difficult. Cerebrospinal fluid (CSF) analysis is of great importance but cytological and biochemical analysis are not entirely specific. Conventional microbiological methods, including Gram stain, antigen detection, and culture are either poorly sensitive or take a long time for a final result.[1,2] The use of molecular biology methods has contributed to improve this scenario with more sensitive and rapid diagnoses.[3]

FilmArray meningitis/encephalitis (ME) panel is a multiplex polymerase chain reaction (PCR) for rapid identification of 14 pathogens from CSF: *Streptococcus pneumoniae*, *Streptococcus agalactiae*, *Escherichia coli K1*, *Haemophylus influenza*, *Listeria monocytogenes*, cytomegalovirus, enterovirus, herpes simplex 1 and 2, human herpesvirus 6, human parechovirus, varicella-zoster virus, and *Cryptococcus neoformans/gattii* (bioMérieux S.A., Marcy l'Étoile, France).[4] The CSF volume used in each

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Table 1 – Cytological and biochemical results in CSF samples obtained from patients with meningitis in which the only positive microbiological result was achieved with FilmArray.

FilmArray	WBC[a] count	Neutrophils (%)	Protein (mg/dl)	Glucose (mg/dl)	Lactate (mg/dl)
S. Pneumoniae	970	70	140	27	63,7
S. Pneumoniae	8000	86	513	5	138,6
S. Pneumoniae	8789	77	475	32	144
S. Pneumoniae	18000	95	229	5	122,7
S. Pneumoniae	250	62	417	62	102
S. Pneumoniae	280	58	427	49	100,7
S. Pneumoniae	110	79	77	51	28,4
S. Pneumoniae	14080	92	270	16	167,9
N. meningitidis	410	38	95	23	24,6
N. meningitidis	6800	89	330	5	96,9
N. meningitidis	6160	75	166	56	70,4
L. monocytogenes	874	42	42	32	69.3
H. influenzae	1706	74	74	75	51.3
H. influenzae	2960	90	90	5	68.5
H. influenzae	5413	80	80	5	110

[a] White blood cells (/mm^3).

reaction is 200 μL, and the run turnaround time is about one hour. In the present study we describe the results obtained with the use of FilmArray ME panel in cases in which bacteria were identified with this method.

This study was conducted between October 2018 and May 2019 and included all cases of suspected meningitis and encephalitis with inflammatory CSF that were collected in private hospitals in São Paulo, Brazil, and sent to Senne Líquor Diagnóstico for CSF analysis. All samples were obtained in emergence rooms. During this period of time all the samples from suspected community-acquired CNS infection cases with at least 10 cells/mm^3 were systematically submitted to FilmArray. Age and sex were recorded. CSF data included leukocytes count, protein, glucose, and lactate determination. Conventional microbiological analysis included Gram stain, bacterial culture, and antigen detection. The results are reported as percentages or mean ± SD.

Four hundred thirty-six CSF samples from 436 patients were submitted to FilmArray. Twenty-five cases (5.7 %) were positive for bacteria. The mean age was 32.7 ± 29.4 years, 13 (52 %) females. *Streptococcus pneumoniae,* the most frequent bacterium, was identified by FilmArray in 12 cases (48 %), followed by *Neisseria meningitidis* in 7 (28 %), and *Haemophylus influenza* in 4 (16 %). *E. coli* and *Listeria monocytogenes* were identified in one case each and no cases were positive for *Streptococcus agalactiae*. Eigth cases (66.6 %) identified as *Streptococcus pneumoniae* were positive only with FilmArray and were negative with Gram stain, culture and antigen detection. Three cases identified as *Neisseria meningitidis* (42.8 %) were positive only with FilmArray. Three (75 %) *Haemophylus influenza* out of the four positive cases with FimArray were negative with other microbiological methods. The *Listeria monocytogenes* case was positive only with FilmArray, whereas the *E.coli* case was positive with FilmArray and culture. CSF cytological and biochemical results of cases in which FilmArray was the only positive method for bacteria identification are shown in Table 1. All these cases had CSF cytological and biochemical results compatible with bacterial meningitis. Ten (40 %) out of the 25 FilmArray positive cases were positive with at least one of the conventional microbiology tests. Culture was positive in 24 % and bacterioscopy in 25 % of those cases. One hundred seventy-four (40 %) of the 436 samples were positive for virus, being enterovirus-77 %, HHV-6-9 %, HSV-2-6 %, VZV-5 %, HSV-1-2 %, and CMV-1 %. One sample was positive for *C. neoformans*. Data on virus and fungal infections were not analyzed in detail in the present study.

The present data suggest that FilmArray enhances the sensitivity for the diagnosis of bacterial meningitis. An alternative explanation is that cases that were positive only with FilmArray are indeed false positive. In fact, this is unlikely since all the 15 cases positive with FilmArray and negative with other microbiological methods had CSF general analysis suggestive of bacterial etiology. It could be argued that the low culture sensitivity is due to previous antibiotic use. Although we do not have detailed clinical information about the patients' treatments, all of the samples were obtained in emergence rooms and therefore likely before initiation of antibiotics. Another possibility for the low sensitivity could be poor quality of the conventional microbiological analysis. However, this is unlikely since these samples were processed in a laboratory specialized in CSF, with all the certifications to carry out high standard microbiological analysis with qualified personnel.

Our results are in line with previous publications. It has been shown that FilmArray enhances pathogen identification in patients with meningitis with negative Gram stain.[5] FilmArray was shown to be efficatious in detecting bacterial etiology in meningitis cases in which CSF culture was negative.[6,7] A previous report showed rapid detection of *Listeria monocytogenes* in a patient in which CSF Gran stain and culture were negative, as occurred in a case in our series.[8] A large study showed high sensitivity and specificity levels. The sensitivity was 85.7 % for HHV-6, 95.7 % for enterovirus and 100 % for all the other agents. The specificity was above 99 % for all the 14 agents.[9] Some studies have showed that FilmArray is cost-effective with a reduction in hospitalization time due to rapid identification of etiologic agent.[10–12]

Our study has limitations that deserve to be mentioned. The study was not designed to assess sensitivity and specificity. Our data do not allow us to conclude about cost-effectiveness as well as length of hospital stay. Therefore, we were not able to assess the overall impact of the utilization of FilmArray. However, we could detect the importance of FilmArray in individual cases, as illustrated in the case in which *Listeria monocytogenes* was identified and could be treated with a specific antibiotic regimen thanks to FilmArray identification. In cases like this, it is reasonable to suppose that the use of this test, which costs around US 350–400, may be cost effective.

In conclusion, FilmArray may allow for a rapid diagnosis of bacterial meningitis, being possibly more sensitive than conventional methods for identifying the bacteria tested in the panel.

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