Burden of pediatric central nervous system infection and cost-benefit simulation of multiplex PCR in Japan

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Summary

To investigate the clinical use of multiplex polymerase chain reaction (mPCR) in Japan, epidemiological and clinical data for central nervous infections are needed. Here we report on the epidemiology and economic burden of central nervous system infections and a simulation of cost-benefit analysis of the FilmArray® Meningitis/Encephalitis (FAME) test for possible clinical use in Japan. We performed FAME test on samples from 27 patients with pleocytosis aged between 0 and 20 years seen in six community hospitals in Nara and Osaka prefectures. All clinical management had been performed without knowledge of the mPCR test results. We analyzed the clinical data and calculated the needed reduction in average length of stay for the FAME test to be cost-beneficial. Among the 27 cases, the FAME test revealed causal pathogens in 13 cases (48.1%). The average medical and social costs per case were ¥299,118 ($2,719.2) and ¥171,768 ($1,561.5), respectively. The minimal needed reduction in average length of stay for the FAME test to be cost-beneficial was 0.32-0.86 day per meningitis case. The result can be informative to evaluate the cost-effectiveness of clinical use of the FAME test in Japan.
Introduction

Bacterial meningitis is a life-threatening condition that requires urgent treatment, whereas viral meningitis is usually self-limiting. Although bacterial meningitis is very rare compared with viral meningitis, partly because of vaccines such as the pneumococcal conjugate vaccine (PCV) and the *Haemophilus influenzae* type B (Hib) vaccine, many children with meningitis are hospitalized and treated with antimicrobials anyway because of the severity of bacterial meningitis, a lack of accurate and timely pathogen diagnosis, and a lack of evidence that they can be safely managed without antimicrobials (1). Therefore, the use of rapid molecular diagnostic techniques, such as a multiplex polymerase chain reaction (mPCR) test to determine the causative agent of meningitis, could make a significant contribution to more appropriate and timely treatment without the need for a hospital stay or the use of antimicrobials. For example, obtaining timely results to ascertain enterovirus or parechovirus infection can contribute to a reduction in both the time spent in hospital and the use of antimicrobial treatment (2). Another study revealed that the use of mPCR tests also led to a reduction in the duration of antimicrobial treatment (3).

To reduce length of hospital stay and unnecessary antimicrobials in cases of viral meningitis in Japan, epidemiological and clinical data relating to meningitis in
conjunction with accurate microbiological diagnosis are needed. In Japan, few tests to rapidly diagnose causative agents of meningitis are currently available on a commercial basis, and the majority of Japanese community hospitals do not have in-house PCR testing facilities. While bacterial culture is the gold standard method for diagnosing pathogens, it usually takes days to get final results. In some cases, cerebrospinal fluid (CSF) samples are sent to research laboratories or regional institutes for public health for pathogen identification, which takes a significant amount of time.

Non-culture methods, including mPCR could contribute to the rapid diagnosis and appropriate treatment of central nervous system (CNS) infections. The FilmArray® Meningitis/Encephalitis (FAME) panel (BIOFIRE/bioMérieux, Salt Lake City, UT, USA) is an mPCR test which can detect fourteen types of pathogen that commonly cause infections of the CNS (Table 1), with a turnaround time of approximately one hour and 90% of sensitivity and 97% of specificity (4). The mPCR test requires just 0.2 ml CSF per test. Some previous studies in other countries have already demonstrated the clinical and economic effectiveness of using FAME panels for pediatric meningitis (2,3,5). However, the diagnostic environment, including the availability of other rapid molecular tests and the type of support offered by the local health care system, such as reimbursement and length of stay, vary considerably by country and region. Before
considering the introduction of new tests in Japan, more data about the epidemiology and disease burden of CNS infections in the post-vaccine era are needed to analyze the cost-effectiveness of these tests. To investigate its possible cost-effectiveness in pediatric CNS infection cases, we retrospectively used the FAME panel assay for pediatric CNS infection cases and performed a simulation of cost-benefit analysis in Japan.

**Material and Methods**

**Design and Setting**

We performed the FAME panel assay on CSF samples from patients aged between 0 and 20 who were diagnosed as CNS infection with pleocytosis in six community hospitals in Nara and Osaka prefectures between September 2017 and May 2019. The cut-off for pleocytosis was a CSF white blood cell (WBC) count >22 cells/µl at <1 month of age; >15 cells/µl at 1–2 months of age; or >5 cells/µl at ≥2 months of age (based on values obtained from a previous article) (6). Exclusion criteria were patients who had received neurosurgery, patients without pleocytosis, and patients whose parents did not give consent. Both consent and assent forms were obtained for all eligible participants prior to lumbar puncture being performed. All clinical management was
performed without medical staff being aware of the results of the mPCR tests. No hospitals included in the study had any in-house rapid PCR testing facilities. Some hospitals could send samples to a regional institute for public health; however, it took approximately 2 to 3 months for clinicians to get the results. Tests performed in regional institutes for health included viral culture and PCR tests, including for mumps (Japan is currently experiencing a mumps epidemic due to the lack of routine vaccination for this disease). Approval from the Institutional Review Boards of all six hospitals was obtained before beginning the registration of participants.

Next, we investigated the epidemiology and disease burden of the participants. We reviewed the participants’ clinical data. We also looked at the diagnostic rate of microorganisms by mPCR compared with conventional tests (culture, antigen and antibody tests, and batched PCR tests). Then, we performed a cost-benefit analysis from a payer’s (governmental) perspective to evaluate the possible cost-effectiveness of the FAME panel assay for future clinical use in Japan.

Cost-benefit analysis

We evaluated the economic burden of study participants. The estimation of economic burden was based on calculating both medical and social costs. If a patient
was managed only as an outpatient, we calculated the medical cost from the patient’s electronic medical record. If a patient was hospitalized, we calculated the hospitalization cost according to the Diagnosis Procedure Combination system (DPC system; a Japanese medical reimbursement system based on length of stay and clinical diagnosis). The social cost, defined as parents’ absence from work, was calculated by the time needed for family members to take care of their hospitalized children, because most pediatric wards in Japan require that one family member accompanies their child throughout their hospitalization. The time of parental absence from work to take care of their hospitalized children was converted to a monetary value by multiplying the time spent by the average daily wage in Japan (7). For the medical cost in hospitalized cases, outpatient and antimicrobial costs were not included because these are not reimbursed in the DPC system. Japanese yen (JPY) were converted into United States dollars (USD) at the rate of 110 JPY per 1 USD.

A cost-benefit ratio (the proportion of the total cost potentially saved by the test to the incremental cost by the test) from a payer’s (governmental) perspective was used as a simulation of the future cost-effectiveness. If the ratio is higher than 1.0, the test is considered as cost-beneficial. In this study, the cost-benefit ratio was calculated by
Cost benefit ratio = the cost potentially saved by the test per meningitis case / the incremental cost by the test per meningitis case

Using the average medical and social costs per one day hospital stay among participants, the cost potentially saved by the calculated as

The cost potentially saved by the test = the potential reduction in length of stay of the test (days) x the average total cost (medical and social costs) per day per case

Then, the needed reduction in average length of stay per meningitis case for the FAME test to be cost-beneficial was calculated. Because the governmental reimbursement of the FAME test has not been established yet, the cost for the respiratory panel was referred as the incremental cost per one FAME test (9,630-25,600 JPY) (8,9). All statistical analyses were performed using Stata 14 (StataCorp. 2015, Stata Statistical Software: Release 14, College Station, TX: StataCorp LP, USA) and Microsoft Excel 2016 (Redmond, WA, USA).

Results

A total of 27 patients were included over the course of the study period. The participants’ backgrounds, clinical courses, and economic burdens are shown in Table 2. The median age of the participants was 6.0 (0.0–14.7) years, and length of stay was 13.0 (7.0–37.8)
days. All participants were managed as inpatients. Of the 27 patients, 23 (85.2%) had received a clinical diagnosis of meningitis, 2 (7.4%) had encephalitis, and 2 (7.4%) had acute flaccid paralysis (AFP). In terms of clinical outcome, all but two of the patients with the CNS infections experienced a complete recovery from their symptoms, while one patient with encephalitis and one with AFP experienced minor neurological sequelae. Antimicrobials were administered to 22 patients (median days of therapy: 7.3 [4.1–17.8] days) and antivirals were administered to 12 patients (median days of therapy: 8.7 [3.7–13.5] days).

The pathogens identified by conventional tests and the FAME panel tests are shown in Table 3. The FAME panel test identified pathogens from 13 cases (48.1%) among the 27 participants (enteroviruses in 10 patients, varicella-zoster virus (VZV) in two patients, and Listeria monocytogenes in one patient). A discrepancy in results occurred in one case (FAME: VZV; conventional PCR: human herpesvirus (HHV) 6B). The discrepancy has not impacted our cost-beneficial calculation. Fifteen CSF samples were sent to regional institutes for public health for conventional testing. No in-house or rapid PCR tests, except for the FAME panel assay, were performed in any of the hospitals throughout the study period. Of 23 meningitis cases, only one was bacterial meningitis. This was a one-year-old girl who had presented with fever and lethargy. The patient was first empirically
treated with meropenem and cefotaxime. The following day her CSF culture sample grew *Listeria monocytogenes*. Therefore, her antimicrobial treatment was switched to ampicillin. Although her fever persisted for weeks, she was discharged without any neurological complications following antimicrobial treatment.

Of the 27 CNS infection cases, the average medical and social costs per one case were ¥299,118 ($2,719.2) and ¥171,768 ($1,561.5), respectively. Among the 23 meningitis patients, the average medical and social costs per one case were ¥245,994 ($2,236.3) and ¥161,270 ($1,466.1), and the average total cost per one day hospital stay was ¥29,831 ($271.2). The minimal needed reduction in average length of stay for the FAME test to be cost-beneficial was 0.32-0.86 day per meningitis case.

**Discussion**

Our study found that the FAME panel could identify the pathogens in approximately 50% children with CNS infection. Compared with previous studies in other countries, our study revealed that children with CNS infections in Japan received longer treatment with antimicrobials and length of stay (1-3). This may be due to the paucity of commercially available rapid PCR tests in Japan and the differences in health care systems. Therefore, the impact of the FAME panel assay may be much greater in Japan.
if it becomes accepted for commercial use. The simulation of the cost-benefit analysis highlighted that 0.32-0.86 day of reduction in length of stay would be required for the FAME test to be cost-beneficial. The Japanese Ministry of Health has recently begun a nationwide antimicrobial stewardship plan (10). As part of this stewardship plan, it is recommended that the treatment of viral infections with antimicrobials should be avoided. The FAME panel may potentially help the stewardship program by also promoting testing for viral CNS infections. We did not consider the antimicrobial cost in our cost-beneficial analysis because all participants were hospitalized in our study, in which the antimicrobial cost is not reimbursed in Japan.

Our study revealed one case of bacterial meningitis both by using the FAME panel test and the conventional test (CSF culture). In bacterial meningitis cases, the rapid identification of causal pathogens is crucial for timely treatment using appropriate antimicrobials. Although bacterial meningitis is becoming rarer in Japan due to high coverage rates having been achieved for both the PCV (96.6% for the 1st dose at 6 months in 2016) and the Hib vaccine (97.9% for the 1st dose at 6 months in 2016) (11), any delay in the accurate diagnosis of bacterial pathogens can have a devastating impact on a patient’s outcome. In our study, the cost reduction or health benefit by a rapid
treatment from timely identification of causal pathogen was not considered, which could make the FAME test more cost-effective.

Our study has several limitations. First, the sample size of the study was small. Therefore, it may be difficult to generalize the findings of the study or to suggest that the study reflects the national average for the epidemiology and economic burden of pediatric CNS infections. However, we believe that our study is important for the nation when considering to introduce this new rapid molecular test for CNS infections.

Second, this study included only participants who had pleocytosis; many studies, however, have shown that a significant number of patients with CNS infections do not have pleocytosis, especially neonates and young infants (12-14). Therefore, we would have missed CNS infections that were not associated with pleocytosis. There is no consensus as to whether universal or selective mPCR testing for CNS infections is more cost-effective once the mPCR test has been approved for a commercial use. Although our data cannot be used to develop a universal mPCR test strategy, this study may provide important basic data for the future analysis of selective mPCR testing because clinicians may be more likely to perform the mPCR tests for CNS infections with pleocytosis. Third, our study retrospectively performed the FAME test and the results were not shared with health care providers. Thus, we can only speculate how case
management may have changed if these results were available to clinicians. Therefore, further studies based on more comprehensive data are warranted.

**Conclusion**

The study provided the needed reduction in length of stay once the FAME test is introduced and reimbursed in Japanese health care system. The result can be informative to evaluate the cost-effectiveness of clinical use of the FAME test in Japan.

**Acknowledgements**

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Authorship contribution: TK, HN, RS, MO, AN and SY designed the study; DK, MO and KM performed tests. TK analyzed data and wrote the manuscript; HN, RS, MO,
AN, DK, MO, KM and SY gave technical support and conceptual advice. All authors read and approved the final manuscript.

**Conflict of interest**

The research was funded by BioMérieux/Biofire for reagents and a device of the FilmArray® meningitis/encephalitis test.
References


### Tables 1. Organisms tested by FilmArray® Meningitis/Encephalitis panel

<table>
<thead>
<tr>
<th>Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli K1</em></td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
</tr>
<tr>
<td><em>Neisseria meningitidis</em></td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Enterovirus</td>
</tr>
<tr>
<td>Herpes simplex virus 1</td>
</tr>
<tr>
<td>Herpes simplex virus 2</td>
</tr>
<tr>
<td>Human herpesvirus 6</td>
</tr>
<tr>
<td>Human parechovirus</td>
</tr>
<tr>
<td>Varicella zoster virus</td>
</tr>
</tbody>
</table>

| Yeast                        |
Cryptococcus neoformans/gattii
**Tables 2. Clinical backgrounds and economic data**

<table>
<thead>
<tr>
<th>Background</th>
<th>N=27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>6.0 (0.0-14.7)</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>74.1%</td>
</tr>
<tr>
<td><strong>Clinical diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td>23 (85.2%)</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>2 (7.4%)</td>
</tr>
<tr>
<td>Acute flaccid paralysis</td>
<td>2 (7.4%)</td>
</tr>
<tr>
<td><strong>Blood</strong></td>
<td></td>
</tr>
<tr>
<td>WBC (/μl)</td>
<td>10,000 (5,540-17,428)</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>0.26 (0.02-3.33)</td>
</tr>
<tr>
<td>Procalcitonin (ng/ml)</td>
<td>0.18 (0.11-0.55)</td>
</tr>
<tr>
<td><strong>CSF</strong></td>
<td></td>
</tr>
<tr>
<td>WBC (/μl)</td>
<td>133 (26-397)</td>
</tr>
<tr>
<td>Poly (/μl)</td>
<td>36 (6-152)</td>
</tr>
<tr>
<td>Protein (mg/dl)</td>
<td>61.0 (22.2-132.8)</td>
</tr>
<tr>
<td>CSF/blood glucose ratio</td>
<td>0.56 (0.43-0.73)</td>
</tr>
</tbody>
</table>
Clinical outcomes

Complete resolution 25 (92.6%)
Minor neurological sequelae 2 (7.4%)
Major neurological sequelae 0 (0.0%)
Death 0 (0.0%)

Antimicrobials used 22 (81.5%)

Days of antimicrobial therapy/case (days) 7.3 (4.1-17.8)

Antivirals used 12 (44.4%)

Days of antiviral therapy/case (days) 8.7 (3.7-13.5)

Hospitalization rate 27 (100%)

Length of stay (days) 13.0 (7.0-37.8)

Medical cost/case ¥253,210 (139,110-518,890)

Antivirals cost/case [$2,301.9 (1,264,6-4,717.2)]

Social cost/case ¥153,566 (82,690-446,523)

Social cost/case [$1,396.1 (751.7-4,059.3)]

The values are exhibited as the median value (10th percentile-90th percentile)
CRP; C-reactive protein, CSF; cerebrospinal fluid, Poly; polymorphonuclear leukocyte, WBC; white blood cell
Table 3. Identified pathogens by the conventional and the mPCR test

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Conventional Test</th>
<th>mPCR Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=27</td>
<td></td>
<td>N=27</td>
</tr>
<tr>
<td>Detection of any pathogen</td>
<td>7 (25.9%)</td>
<td>13 (48.1%)</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>4 (14.8%)</td>
<td>10 (37.0%)</td>
</tr>
<tr>
<td>VZV</td>
<td>0 (0.0%)</td>
<td>2 (7.4%)</td>
</tr>
<tr>
<td>HHV 6</td>
<td>1 (3.7%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Mumps</td>
<td>1 (3.7%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>1 (3.7%)</td>
<td>1 (3.7%)</td>
</tr>
</tbody>
</table>

VZV; Varicella-zoster virus, HHV; Human herpesvirus