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Original Research Article

A CROSS SECTIONAL OBSERVATIONAL STUDY ON THE ROLE OF MULTIPLEX PCR IN DIAGNOSIS OF CNS INFECTION AT SMS MEDICAL COLLEGE AND ASSOCIATED HOSPITALS

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ABSTRACT

Background: Central nervous system (CNS) infections in children are medical emergencies associated with high morbidity and mortality. Early etiological diagnosis is crucial for timely targeted therapy, yet conventional diagnostic methods such as cerebro spinal fluid (CSF) culture have limited sensitivity, especially in partially treated cases. Multiplex polymerase chain reaction (PCR) assays offer rapid detection of multiple pathogens and may improve diagnostic yield in pediatric CNS infections.

Materials and Methods: This cross-sectional observational study was conducted in the Department of Paediatrics at SMS Medical College and its associated hospitals, Jaipur. A total of 110 children aged 6 months to 18 years with clinical features suggestive of meningitis or encephalitis were enrolled. CSF samples were analyzed using the BioFire FilmArray Meningitis/Encephalitis multiplex PCR panel in addition to conventional microbiological testing. Demographic, clinical, laboratory, neuroimaging, and microbiological data were recorded and analyzed using SPSS software. Diagnostic performance and etiological profiles were assessed.

Results: The majority of patients were aged 1–5 years (48.18%), with a mean age of 4.15 ± 3.82 years. Fever (100%) and seizures (90%) were the most common clinical features. CSF culture was sterile in 68.19% of cases. The BioFire multiplex PCR panel detected pathogens in 27.27% of patients, identifying both bacterial and viral etiologies. Gram-negative organisms predominated in culture-positive cases. Among PCR-negative patients, a significant proportion were diagnosed with autoimmune or non-infectious conditions such as acute disseminated encephalomyelitis and autoimmune encephalitis. Culture and PCR demonstrated complementary diagnostic roles.

Conclusion: Multiplex PCR significantly enhances early etiological diagnosis of pediatric CNS infections, particularly in culture-negative or partially treated cases. However, conventional CSF culture remains essential for antimicrobial susceptibility testing and detection of pathogens outside PCR panels. An integrated diagnostic approach combining molecular, microbiological, neuroimaging, and immunological evaluation is necessary for optimal management.

Keywords: Central nervous system infection; Pediatrics; Multiplex PCR; BioFire FilmArray; Meningitis; Encephalitis; Cerebrospinal fluid etc.

INTRODUCTION

Central nervous system (CNS) infections, including meningitis and encephalitis, represent medical emergencies associated with high morbidity and mortality, particularly in the pediatric population. These infections may be caused by a wide spectrum of pathogens such as bacteria, viruses, fungi, and occasionally parasites. Despite advances in antimicrobial therapy and intensive care, CNS infections continue to result in significant neurological sequelae and death, emphasizing the importance of early and accurate diagnosis.[1]

The global burden of CNS infections remains substantial, especially in low- and middle-income countries. Acute encephalitis syndrome (AES) in children has an estimated incidence of 10.5–13.8 per 100,000, with case fatality rates reported to be as high as 30% in certain regions. Moreover, nearly one-third of survivors develop long-term neurological disabilities.[2] According to the Global Burden of Disease Network, meningitis and encephalitis together accounted for over half a million deaths worldwide in 2010, highlighting the urgent need for improved diagnostic strategies.[3]

The etiological spectrum of CNS infections varies with age, geographical location, immune status, and vaccination coverage. In developed countries, routine immunization has significantly reduced bacterial meningitis caused by Haemophilus influenzae type b and Neisseria meningitides.[4] However, viral pathogens such as enteroviruses, herpes simplex virus (HSV), and arboviruses continue to be major causes of encephalitis globally.[5] In contrast, in resource-limited settings, bacterial meningitis remains common due to limited vaccine coverage, with neonates and young infants particularly susceptible to infections caused by Escherichia coli, Streptococcus agalactiae, and Listeria monocytogenes.[6] Immunocompromised children are at increased risk of opportunistic CNS infections caused by pathogens such as Cryptococcus neoformans and cytomegalovirus (CMV).[7]

Clinical diagnosis of CNS infections is challenging because of overlapping and nonspecific presentations. Symptoms such as fever, seizures, altered sensorium, headache, and neck stiffness are common to both meningitis and encephalitis, making clinical differentiation unreliable.[8] Conventional diagnostic methods, including cerebrospinal fluid (CSF) analysis, Gram staining, and culture, remain the diagnostic cornerstone. However, CSF culture has limited sensitivity, particularly in patients who have received prior empirical antimicrobial therapy, and results may take several days, delaying definitive diagnosis.[9]

In viral CNS infections, especially encephalitis, routine diagnostic techniques often fail to identify the causative pathogen. Viral cultures are time-consuming, and serological tests may be inconclusive in the early phase of illness, leading to prolonged empiric therapy and potentially avoidable adverse effects.[10] Early etiological diagnosis is critical, as delays in appropriate treatment are associated with increased mortality and long-term neurological impairment.[11]

Molecular diagnostic techniques, particularly polymerase chain reaction (PCR), have emerged as valuable tools for the rapid and accurate identification of CNS pathogens. Multiplex PCR assays allow simultaneous detection of multiple bacterial, viral, and fungal pathogens directly from CSF samples and are less affected by prior antimicrobial exposure.[12] The BioFire FilmArray Meningitis/Encephalitis panel is one such multiplex PCR system that detects 14 common CNS pathogens within approximately one hour, significantly improving diagnostic yield and clinical decision-making.[13-15]

The use of multiplex PCR has been shown to facilitate early de-escalation of empirical therapy, reduce unnecessary antibiotic use, shorten hospital stay, and improve outcomes, particularly in pediatric patients.[16-17] However, challenges such as cost, limited availability, and potential overdiagnosis remain, especially in resource-constrained settings.[18-19]

The present study was designed to evaluate the etiological profile and diagnostic utility of multiplex PCR in patients with suspected CNS infections, particularly in partially treated, culture-negative cases, at SMS Medical College and Associated Hospitals, Jaipur.

MATERIALS AND METHODS

This cross-sectional observational study was conducted in the Department of Paediatrics at SMS Medical College and its affiliated hospitals, Jaipur after approval of insitute ethical committee(362/MC/EC/2023 DATE 18/1/2024) . The study was carried out over a defined period until the required sample size was achieved.

The sample size was calculated assuming a 7% positivity rate of the Meningitis/Encephalitis (ME) panel based on previously published data, with a study power of 80% and a confidence level of 95%. Using an absolute allowable error of 5%, the minimum sample size was estimated to be 100 patients. To account for a potential attrition rate of 10%, the final sample size was increased to 110 patients.

Children aged 6 months to 18 years presenting with clinical features suggestive of meningitis or encephalitis were enrolled after applying inclusion and exclusion criteria. Eligible patients included those with a history of prolonged fever (5–10 days) followed by seizures and altered sensorium, and who were not participating in any other clinical study. Patients with irreversible encephalopathy and those whose guardians did not provide informed consent were excluded.

After enrollment, detailed clinical history, physical examination findings, and relevant laboratory investigations were recorded using a structured pro forma. Cerebrospinal fluid (CSF) samples were collected under aseptic conditions in sterile, appropriately labeled containers and promptly transported to the Advanced Microbiology Laboratory at SMS Medical College, Jaipur, for further analysis.

CSF samples were tested using the BioFire FilmArray Meningitis/Encephalitis Panel, a multiplex polymerase chain reaction (PCR) assay capable of simultaneously detecting multiple bacterial, viral, and fungal pathogens associated with CNS infections. The assay was performed according to the manufacturer's instructions. Briefly, the test pouch was hydrated, and a mixture of CSF and sample buffer was prepared and loaded into the pouch. The pouch was then inserted into the FilmArray instrument, where automated nucleic acid extraction, amplification, and detection were carried out, with results generated within approximately one hour.

All collected data were entered into Microsoft Excel and subsequently analyzed using the Statistical Package for the Social Sciences (SPSS) software, version XX (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize demographic, clinical, and laboratory variables. Categorical variables were expressed as frequencies and percentages, while continuous variables were presented as mean ± standard deviation or median with interquartile range, as appropriate. The diagnostic performance of the ME panel was assessed by calculating sensitivity, specificity, positive predictive value, and negative predictive value. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The majority of patients (48.18%) belonged to the 1-5 years age group, with a mean age of 4.15 ± 3.82 years. Male predominance was observed (59.09%), and most patients resided in rural areas (66.36%). The socioeconomic distribution revealed that the lower middle class (34.55%) and upper middle class (30.92%) constituted the majority of the study population. Hindu patients comprised 90.91% of the cohort. The age distribution showed statistically significant variation ($\chi^2 = 40.764$, $p < 0.00001$), as did residence ($\chi^2 = 11.782$, $p = 0.0006$) and socioeconomic status ($\chi^2 = 30.182$, $p < 0.00001$). [Table 1]

Fever was universally present (100%), followed by convulsions in 90% of patients, with generalized convulsions (80%) being more common than focal seizures (10%). Altered sensorium was documented in 42.7% of cases. Meningeal signs including neck rigidity (23.6%), Brudzinski sign (20%), and Kernig's sign (19%) were observed in approximately one-fifth of patients. Cranial nerve involvement was relatively uncommon, with facial nerve palsy being the most frequent (5.4%). The distribution of clinical features was statistically significant ($\chi^2 = 71.5$, $p < 0.001$). [Table 2]

The majority of patients (72.70%) demonstrated normal CSF cell counts (0-5 cells/mm³), while elevated counts (>100 cells/mm³) were observed in only 9.10% of cases. CSF protein levels were within normal limits (<45 mg/dl) in 32.73% of patients, mildly elevated (45-100 mg/dl) in 40.91%, and moderately elevated (100-200 mg/dl) in 24.55%. CSF sugar was reduced (<45 mg/dl) in 35.45% of patients, suggesting possible bacterial or tubercular etiology in these cases. All CSF parameters demonstrated statistically significant distributions ($p < 0.001$). [Table 3]

Neuroimaging abnormalities were detected in 72.73% of cases, while 27.27% had normal MRI findings. Meningoencephalitis was the most common abnormality (24.54%), followed by leptomeningeal enhancement (21.82%) and non-infective/autoimmune etiologies (21.81%). Among meningoencephalitis cases, non-specific T2 hyperintensity with restricted diffusion was most prevalent (14.54%), while imaging patterns suggestive of cytomegalovirus (5.45%) and herpes simplex virus (4.54%) infections were also identified. ADEM and autoimmune encephalitis each accounted for 4.54% of cases. The distribution of MRI findings was statistically significant ($\chi^2 = 22.46$, $p < 0.001$). [Table 4]

CSF culture was sterile in 68.19% of patients, while bacterial pathogens were isolated in 31.81% of cases. Among culture-positive specimens, gram-negative organisms predominated, with Acinetobacter (8.20%) and E. coli (5.45%) being the most common isolates. The BioFire multiplex PCR panel detected pathogens in 27.27% of cases, identifying both bacterial (Streptococcus pneumoniae 4.54%, E. coli 4.54%) and viral agents (Enterovirus 4.54%, HSV-1 4.54%, CMV 3.63%, VZV 2.72%, EBV 2.72%). Among the 80 BioFire-negative patients, possible meningoencephalitis (57.50%), autoimmune encephalitis (20%), and ADEM (20%) were the predominant diagnoses. Concordance analysis between culture and BioFire revealed complementary diagnostic utility, with 17 cases detected exclusively by BioFire and 22 culture-positive cases involving organisms not included in the BioFire panel. All microbiological findings demonstrated statistical significance ($p < 0.001$). [Table 5]

Table 1: Demographic Characteristics of Study Patients (N=110)

Characteristic	Category	Frequency (n)	Percentage (%)
Age Group	≤1 year	32	29.10
	1-5 years	53	48.18
	5-10 years	13	11.82
	>10 years	12	10.90
	Mean ± SD: 4.15 ± 3.82 years; Median: 3.00 years; Range: 0.5-17 years		
Gender	Male	65	59.09
	Female	45	40.91
Residence	Rural	73	66.36
	Urban	37	33.64
Socioeconomic Status	Upper Class	12	10.90
	Upper Middle Class	34	30.92
	Lower Middle Class	38	34.55
	Upper Lower Class	14	12.73
	Lower Class	12	10.90
Religion	Hindu	100	90.91
	Muslim	10	9.09

Table 2: Clinical Presentation of Study Patients (N=110)

Clinical Features	Frequency (n)	Percentage (%)
Symptoms		
Fever	110	100.0
Convulsions (Total)	100	90.0
- Generalized convulsion	89	80.0
- Focal convulsion	11	10.0
Altered sensorium	47	42.7
Rash	22	20.0
Petechiae	20	18.1
Irritability	11	10.0
Signs		
Neck rigidity	26	23.6
Brudzinski sign	22	20.0
Kernig's sign	21	19.0
7th cranial nerve palsy (Facial)	6	5.4
6th cranial nerve palsy (Abducens)	3	2.7
Ataxia	3	2.7
3rd cranial nerve palsy (Oculomotor)	2	1.8
Aphasia	2	1.8

Table 3: Cerebrospinal Fluid Parameters of Study Patients (N=110)

CSF Parameter	Category	Frequency (n)	Percentage (%)
Cell Count (cells/mm³)	0-5	80	72.70
	6-100	20	18.20
	>100	10	9.10
Protein (mg/dl)	<45	36	32.73
	45-100	45	40.91
	100-200	27	24.55
	>200	2	1.81
Sugar (mg/dl)	<45	39	35.45
	45-100	68	61.82
	100-200	3	2.73

Table 4: MRI Findings of Study Patients (N=110)

MRI Findings	Frequency (n)	Percentage (%)
Normal	30	27.27
Abnormal	80	72.73
Meningoencephalitis	27	24.54
- Non-specific T2 hyperintensity with restricted diffusion	16	14.54
- Suspected CMV (periventricular calcification, migrational abnormality)	6	5.45
- Suspected HSV (T2 hyperintensity, vasculopathy, hemorrhage, necrosis)	5	4.54
Leptomeningeal enhancement	24	21.82
Non-infective/Autoimmune etiology	24	21.81
- Non-specific hypodensity/edema	14	12.70
- ADEM	5	4.54
- Autoimmune encephalitis	5	4.54
Abscess	2	1.81
Tubercular meningitis	2	1.81
Bilateral mastoiditis	1	0.90

Table 5: Microbiological Profile and Etiological Diagnosis (N=110)

Investigation	Findings	Frequency (n)	Percentage (%)
CSF Culture			
	Sterile	75	68.19
	Culture Positive	35	31.81
Gram-positive organisms	Enterococcus	8	7.28
	Streptococcus pneumoniae	3	2.72
Gram-negative organisms	Acinetobacter	9	8.20
	E. coli	6	5.45
	Pseudomonas	4	3.63
	Klebsiella	4	3.63
	Burkholderia	1	0.90
CSF BioFire Panel			
	Not Detected	80	72.73
	Detected	30	27.27
Bacterial pathogens	Streptococcus pneumoniae	5	4.54
	E. coli	5	4.54
Viral pathogens	Enterovirus	5	4.54
	Herpes Simplex virus-1	5	4.54
	Cytomegalovirus	4	3.63
	Varicella zoster virus	3	2.72
	Epstein-Barr virus	3	2.72
Etiology in BioFire-Negative Patients (n=80)			
	Possible meningoencephalitis	46	57.50
	Autoimmune encephalitis	16	20.00
	ADEM	16	20.00
	Anti-NMDA receptor encephalitis	2	2.50
Culture-BioFire Concordance Analysis			
	Culture positive only	35	-
	Culture negative, BioFire positive	17	-
	Both Culture and BioFire positive (concordant)	8	-
	Partial concordance (different organisms)	5	-
	Culture positive for organisms not in BioFire panel	22	-

DISCUSSION

In the present cross-sectional observational study involving 110 pediatric patients with suspected central nervous system (CNS) infections, the age distribution was significantly skewed toward younger children, with nearly half of the cohort (48.2%) belonging to the 1–5-year age group and a median age of 3 years. This statistically significant clustering among infants and preschool-aged children underscores the heightened vulnerability of this age group, likely attributable to immature immune responses, increased exposure to infectious agents, and limited prior immunity. Similar age-related patterns have been consistently reported across India and other low- and middle-income countries, where acute CNS infections predominantly affect children under five years of age.[20]

A slight male predominance was observed in the study population (59.1%), although this did not reach statistical significance. This trend has been widely reported in pediatric encephalitis cohorts and may reflect a combination of biological susceptibility and sociocultural factors, including preferential healthcare-seeking behavior for male children in certain communities.[12] While sex-based biological differences in immune response have been proposed, these factors remain incompletely understood and warrant further investigation.

Marked socioeconomic and geographic disparities were evident in this cohort. A significant proportion of patients belonged to lower-middle and upper-middle socioeconomic strata, and two-thirds were from rural areas. These findings highlight persistent inequities in access to healthcare, delayed presentation, and limited diagnostic resources in rural settings. Such disparities have been associated with poorer outcomes, delayed initiation of appropriate therapy, and increased financial burden on families affected by CNS infections.[17,19] The predominance of Hindu patients likely reflects the demographic distribution of the hospital's catchment area rather than any disease-specific association.

Clinically, fever was a universal presenting feature, while seizures were observed in 90% of cases, with generalized seizures being the most common. Altered sensorium was present in approximately 43% of patients. In contrast, classical meningeal signs were observed in only about one-fifth of cases, demonstrating low sensitivity in the pediatric population. This finding reinforces existing evidence that meningeal signs are often absent or subtle in young children, emphasizing the importance of maintaining a high index of suspicion even in their absence.[20-21] The predominance of fever and seizures as presenting features is consistent with prior Indian studies on pediatric CNS infections.

Cerebrospinal fluid (CSF) analysis revealed predominantly non-specific findings. The majority of

patients had low CSF cell counts, moderately elevated protein levels, and normal CSF glucose, collectively suggesting a viral or non-bacterial etiology in many cases. However, these parameters lack diagnostic specificity and often overlap between infectious and non-infectious conditions. Similar CSF profiles have been reported in Indian encephalitis cohorts, particularly in settings where viral etiologies predominate and diagnostic facilities are limited.[16,22]

Neuroimaging findings further illustrated the diagnostic complexity of pediatric CNS infections. Abnormalities were detected in nearly three-quarters of patients, including features suggestive of meningoencephalitis, leptomeningeal enhancement, and autoimmune involvement, while over one-quarter of scans were normal. These overlapping imaging patterns reflect the challenge of differentiating infectious from autoimmune or post-infectious etiologies based on radiology alone, especially in the acute phase.[14]

Microbiological confirmation using conventional methods remained limited. CSF cultures were sterile in more than two-thirds of cases, likely due to prior antibiotic exposure, fastidious organisms, or non-bacterial etiologies. Notably, Gram-negative organisms such as Acinetobacter and Escherichia coli were more frequently isolated than traditionally dominant pathogens like Streptococcus pneumoniae. This shift may reflect increasing healthcare-associated infections, antimicrobial resistance, and changing epidemiology within Indian hospital settings, consistent with regional reports.[22]

The use of the BioFire multiplex PCR panel improved diagnostic yield, identifying etiological agents in 27.3% of cases. Both bacterial and viral pathogens were detected, including S. pneumoniae, E. coli, enteroviruses, HSV-1, CMV, VZV, and EBV. Nevertheless, the majority of samples remained negative, underscoring the inherent limitations of panel-based molecular diagnostics, which target a predefined set of pathogens and may miss uncommon, emerging, or non-infectious causes. Similar detection rates have been reported in Indian studies, where multiplex PCR positivity often remains below 40%.

Importantly, among BioFire-negative cases, a substantial proportion were subsequently diagnosed with autoimmune etiologies, including acute disseminated encephalomyelitis, autoimmune encephalitis, and anti-NMDA receptor encephalitis. This finding highlights the growing recognition of immune-mediated CNS disorders in children and emphasizes the need to consider non-infectious causes when microbiological investigations are inconclusive.[14] Early identification of these conditions is crucial, as they require fundamentally different therapeutic approaches.

Analysis of concordance between CSF culture and multiplex PCR revealed significant discordance, with a notable proportion of culture-positive cases testing negative on PCR. This observation reinforces the complementary nature of conventional and molecular diagnostics, particularly in resource-limited settings where reliance on a single modality may result in missed diagnoses.

Overall, this study demonstrates that pediatric CNS infections in India are shaped by age-related susceptibility, socioeconomic and rural–urban disparities, evolving pathogen profiles, and an increasing contribution of autoimmune etiologies. Strengthening diagnostic capacity in rural areas, integrating multiplex PCR with conventional microbiology and immunologic testing, and enhancing clinician awareness of non-infectious causes are essential steps toward improving outcomes. Such integrated diagnostic strategies are critical for reducing morbidity and mortality associated with pediatric CNS infections and align with broader global public health priorities aimed at improving child health outcomes.

CONCLUSION

The BioFire Meningitis/Encephalitis panel enhances early etiological diagnosis in pediatric CNS infections by enabling rapid detection of common pathogens, particularly in partially treated or culture-negative cases. However, conventional CSF culture continues to play a crucial role in identifying organisms not included in the PCR panel and in guiding antimicrobial susceptibility–based therapy. In addition, the substantial proportion of children diagnosed with autoimmune or non-infectious CNS disorders underscores the need for an integrated diagnostic strategy that combines molecular testing with conventional microbiology, neuroimaging, and immunological evaluation.

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