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Optimizing Early Diagnosis of Pediatric Meningitis: Role of Methods and complementary Biomarkers

Fatma M. Helbawi[1], Heba G. Rashed [1], Doha Fahmy Mohamed[1], Asmaa O. Ahmed [1], Aml A. R. Mohammed[1]

[1] Department of Clinical pathology, Faculty of Medicine, Assiut University, Assiut, Egypt

1- Fatma Mohammed Helbawi Mohammed
e-mail: Fatmahelbawi@aun.edu.eg
2- Heba-tallah Gamal El-din Rashed
3- Doha Fahmy Mohamed
4- Asmaa Omar Ahmed
5- Aml Adel Rayan Mohammed
e-mail: amladel@aun.edu.eg

Abstract

Infections of the central nervous system (CNS) continue to represent a major global health threat due to their significant mortality rates. Bacterial meningitis remains among the most critical and life-threatening infections worldwide, particularly in the absence of timely treatment, where mortality may reach up to 50%. Early and accurate identification of the type of meningitis is essential to guide appropriate therapeutic interventions and to improve clinical outcomes. This study was designed to evaluate the effectiveness of various diagnostic methods for meningitis and to identify the most frequently encountered causative organisms.

This cross-sectional, hospital-based observational study was conducted at Assiut University Children's Hospital in collaboration with the microbiology unit of the Clinical Pathology Department, Faculty of Medicine, Assiut University, between November 2019 and September 2020. A total of 48 children, between the ages of 2 and 9 who had convulsions, fever, or a disturbed state of consciousness—all of which are

clinical indicators of meningitis—were included. A thorough physical examination, clinical history, and detailed demographic information were all documented. Serum C-reactive protein (CRP), cerebrospinal fluid (CSF) CRP, serum procalcitonin (PCT), and multiplex PCR testing were among the standard and specialized laboratory procedures used in the investigations.

Conclusion: In clinical practice, it is still difficult to distinguish between bacterial and viral meningitis. According to the study's findings, multiplex PCR had the best diagnostic accuracy, followed by serum PCT, CSF CRP, and CSF/blood glucose ratio.

Keywords: Pediatric meningitis, CSF, CRP, PCT, multiplex PCR.

Introduction

The central nervous system (CNS) can be invaded by a variety of infectious agents, such as bacteria, viruses, fungi, and parasites. This can lead to clinical syndromes such meningitis, encephalitis, brain abscesses, subdural empyema, and septic thrombophlebitis. Particularly in underdeveloped nations, these CNS diseases are linked to significant morbidity and mortality. With a high morbidity and mortality rate, bacterial meningitis - one of the most serious CNS infections - continues to pose a threat to world health. Known as septic meningitis, it can kill up to 50% of patients if left untreated **(1).** Children are particularly susceptible, and it can be challenging to distinguish between bacterial and viral meningitis in the early stages. However, making this distinction is essential to starting an effective treatment. Bacterial meningitis kills an estimated 135,000 children worldwide each year, affecting about 1.2 million people **(2).**

Mortality rates vary greatly, from 4.5% in industrialized nations to as high as 15–50% in resource-limited environments. In contrast, viral infections of the CNS are less common and often result in aseptic meningitis or meningoencephalitis, while pure encephalitis can occur rarely. In low-resource pediatric communities, meningitis-related mortality can still approach 40% after therapy **(3).**

Molecular diagnostic techniques, such as the BIOFIRE® FILMARRAY® multiplex PCR system, have significantly improved the rapid identification of microbial nucleic acids. This FDA, CE-IVD, and TGA-certified system offers fully integrated sample preparation, amplification, detection, and analysis with minimal hands-on time and results in approximately one hour. PCR testing offers greater sensitivity than conventional culture methods, particularly in patients who have already received antibiotic therapy **(4).**

Aim of the Study

To assess the diagnostic performance of various laboratory methods in identifying meningitis in children and to determine the most frequently detected causative pathogens.

Materials and Methods

Study Design and Population

This study employed a cross-sectional, observational design. It was conducted at Assiut University Children's Hospital between November 2019 and September 2020, specifically in the Microbiology Unit of the Clinical Pathology Department, Faculty of Medicine, Assiut University. The study included 48 pediatric patients aged 2 to 9 years who presented to the Pediatric Emergency Unit with clinical signs indicative of meningitis—fever, altered consciousness, and/or seizures. Informed oral consent was obtained from the parents or guardians of all participants. The study protocol was reviewed and approved by the ethical committee of the Faculty of Medicine, Assiut University.

Clinical and Laboratory Data Collection

Detailed demographic and clinical data were gathered, including age, sex, and any pre-existing medical conditions. All patients underwent a thorough medical history assessment focusing on meningitis-related symptoms—such as fever, seizures, altered mental status, and meningeal signs—as well as any prior antibiotic use (type, dose, duration, and timing).

Laboratory Investigations

Routine Tests:

- Complete Blood Count (CBC) with differential was performed on ADVIA 2120i automated hematology analyzer (Siemens healthineers, Bavaria, Germany).
- Serum C-reactive protein (CRP), lactate dehydrogenase (LDH), electrolytes (sodium, potassium and calcium), renal function tests (urea, creatinine) and blood glucose levels were measured prior to lumbar puncture using chemiluminescence method on Advia 1800 automated analyzer (Siemens healthineers, Bavaria, Germany).

Specific Tests:

- Cerebrospinal fluid (CSF) analysis (microscopic, chemical, and microbiological)
- Biomarker evaluation
- Molecular testing (Multiplex PCR)

CSF Sampling Protocol

Lumbar puncture was performed under sterile conditions, and 5 mL of CSF was collected and distributed as follows:

- 1ml in a plain tube for macroscopic appearance and microscopic examination using the Hemocytometer.
- 2 ml in a plain tube with sodium citrate for biochemical tests and biomarkers.
- 2 ml in a sterile tube for culture and PCR analysis.

Measurement of CSF biochemical tests and biomarkers:

- Biochemical tests (protein and glucose) were analyzed on Dimension Expand (Siemens healthineers, Bavaria, Germany).
- CSF CRP was measured using enzyme-linked immunosorbent assay (ELISA) (Human CRP ELISA Kit, SinoGeneClon Biotech Co., Ltd, China, Cat. No: SG-00451).
- Serum Procalcitonin (PCT) was measured using ELISA (Human PCT ELISA Kit, SinoGeneClon Biotech Co., Ltd, China; Cat. No: SG-10689).

Microbiological culture:

Each CSF sample was inoculated under aseptic conditions into blood culture bottle of automated blood culture (Bact/Alert, bioMérieux SA, Marcy- l'Etoile, France) for 5 days for negative results. The positive bottles were inoculated on the media; one blood agar plate, one pre-warmed chocolate agar plate, one MacConkey agar plate, sabauroud's agar plate and one tube of sterile enrichment broth for each sample. The chocolate agar plate was placed in the CO2 jar with added 5-10% CO2 pack and incubate at 36°C±1 °C for 18-48 hours. The blood agar and the MacConkey agar plates were incubated at 36°C±1°C for 18-48 hours under aerobic conditions. 2 plates of sabaroud's agar were incubated; one at 25°C and the other at 37°C. Microscopic examination by gram stain from the growth colonies were performed. Bacterial identifications were performed by using the Vitek2® compact system (bioMérieux SA, Marcy- l'Etoile, France) according to its manual instruction.

Molecular testing:

Multiplex PCR was done for each sample using the BIOFIRE® FILMARRAY® system (BioFire Diagnostics, LLC, Salt Lake City, USA) according to the manufacturer's instructions.

Statistical Analysis

Data was analyzed using SPSS (Statistical Package for the Social Science, software, version 20, IBM, Armonk, NY). Continuous variables were expressed as mean ± standard deviation (SD) or median values. Categorical variables were presented as frequencies and percentages. The Chi-square test (χ^2) was applied to compare categorical data between bacterial and viral meningitis cases. The Student's t-test was used to compare means between two groups. Receiver Operating Characteristic (ROC) curve analysis was used to assess the diagnostic performance of serum CRP, serum LDH, serum PCT, CSF CRP, and multiplex PCR. A confidence interval (CI) of 95% was maintained, and P-values < 0.05 were considered statistically significant.

Results

Mean age of enrolled patients was 3.27 ± 1.27 years with a range between two and nine years. Out of those patients, 34 patients (70.8%) were 2- 4 years, 11 patients (22.9%) were 4- 6 years, 3 patients (6.3%) were 6- 9 years, and respectively. 29 patients (60.4%) were males while the other 19 patients (39.6%) were females, respectively.

From the bottle of positive blood culture was noticed that 20 samples out of 48 samples (41.6%) showed positive bacterial growth in CSF cultures, and 28 samples (58.4%) showed no growth. While it was noticed that 27 samples out of 48 samples (56.2%) showed positive results in organism detection and 21 samples (43.8%) showed negative results by multiplex PCR.

The most frequent organism detected by blood culture and multiplex PCR was Streptococcus pneumoniae in 9 samples (18.8%) and 8 samples (16.7%) respectively, **table 1,2**.

Table 1: Culture of the cerebrospinal fluid among enrolled patients

❖ **CSF culture result & type of**	**Total sample number** N= 48

organism	
• **Positive growth**	Total 20 sample
Streptococcus pneumoniae	9 (18.8%)
Neisseria meningitidis	4 (8.3%)
Haemophilus influenzae	3 (6.3%)
Klebsiella pneumoniae	2 (4.2%)
Staph.aureus	2 (4.2%)
• **No growth**	28 sample (58.4%)

Data expressed as frequency (percentage).

Table 2: Type of organism based on multiplex PCR among enrolled patients

❖ **Type of organism**	**Total sample number** N= 48
• **Positive results**	Total 27 sample
Streptococcus pneumoniae	8 (16.7%)
Enetroviruses	6 (12.5%)
Herpes simplex virus	6 (12.5%)
Neisseria meningitidis	4 (8.3%)
Haemophilus influenza	3 (6.3%)
• **Negative results**	21 sample (43.8%)

Data expressed as frequency (percentage).

Thirty-two samples out of the total collected samples (N=48) had meningitis. 20 samples (62.5%) of the 32 positive samples had bacterial meningitis and 12 samples (37.5%) had viral meningitis, **table 3**.

Table 3: Characteristics of patients based on final diagnosis

	Viral meningitis (n= 12)	**Bacterial meningitis** (n= 20)	**P value**
Age (years)	2.65 ± 1.06	3.50 ± 1.28	**0.03**
Sex: - Male - Female	 6 (46.2%) 7 (53.8%)	 23 (65.7%) 12 (34.3%)	 0.18
Presentation			
Fever: - High grade - Low grade	 0 12 (100%)	 12 (60%) 8 (40%)	 < **0.001**
Disturbed conscious level	8 (61.5%)	35 (100%)	< **0.001**
Convulsion	11 (84.6%)	27 (77.1%)	0.44
Increased ICP	0	8 (22.9%)	0.06
Lab investigation			

Blood glucose (mg/dl)	91.38 ± 40.21	121.08 ± 55.12	0.08
Leucocytes (10^3/ul)	13.76 ± 6.28	8.97 ± 6.54	0.79
Platelets (10^3/ul)	349.07 ± 128.36	387.58 ± 125.08	0.99
Neutrophil (10^3/ul)	7.21 ± 1.60	5.56 ± 1.23	0.35
Lymphocytes (10^3/ul)	2.3 ± 1.14	3.19 ± 1.42	0.30
Serum Sodium (mmol/l)	138.16 ± 2.43	138.30 ± 4.31	0.39
Serum potassium (mmol/l)	4.45 ± 0.33	4.54 ± 0.64	0.80
Serum calcium (mg/dl)	8.43 ± 1.54	8.54 ± 1.54	0.62
Serum urea (mg/dl)	6.64 ± 2.80	5.77 ± 2.30	0.98
Serum creatinine (mg/dl)	0.98 ± 0.12	1.31 ± 0.14	0.57
Serum CRP (mg/dl)	17.03 ± 10.97	43.46 ± 12.45	**0.03**
Serum LDH (u/l)	123.30 ± 19.71	232.65 ± 57.09	**0.04**
Procalcitonin (ng/dl)	1.10 ± 0.20	1.98 ± 0.14	< **0.001**
CSF examination:			
Protein (mg/dl)	40.19 ± 24.85	94.65 ± 23.45	< **0.001**
Glucose (mg/dl)	50.50 ± 9.72	38.28 ± 15.98	**0.01**
CRP (pg/ml)	0.14 ± 0.06	0.71 ± 0.37	< **0.001**
Total cells (cells/mm^3)	817.53 ± 45.78	2565.87 ± 543.12	< **0.001**
Neutrophil (cells/mm^3)	253.07 ± 102.34	2122.85 ± 385.45	< **0.001**
Lymphocytes (cells/mm^3)	575.23 ± 185.13	437.14 ± 213.45	0.37
Predominant cells in CSF:			
Polymorphonuclear cells	0	20 (48%)	< **0.001**
Lymphocytes	12 (25%)	0	
CSF/blood glucose ratio	0.58 ± 0.25	0.25 ± 0.09	< **0.001**

Data expressed as mean (SD), frequency (percentage).
ICP: intracranial pressure, CRP: C-reactive protein, LDH: Lactate dehydrogenase, CSF: cerebrospinal fluid

The sensitivity (true positive results), it was found that CRP-CSF and CSF/blood glucose ratio had the best sensitivity (80%) among all markers followed by serum LDH and serum PCT level equal sensitivity (69%), while serum CRP is the least one in sensitivity (60%). But **the specificity** (true negative results) was higher in serum CRP (100%) than CRP-CSF (92.3%) and equal in other marker (serum LDH, serum PCT (85%) and CSF/blood glucose ratio (84%)) while, **the overall accuracy** was the best in CRP-CSF (82.3%), CSF/blood glucose ratio (81.1%) then serum PCT (73.3%), respectively, Figure 1.

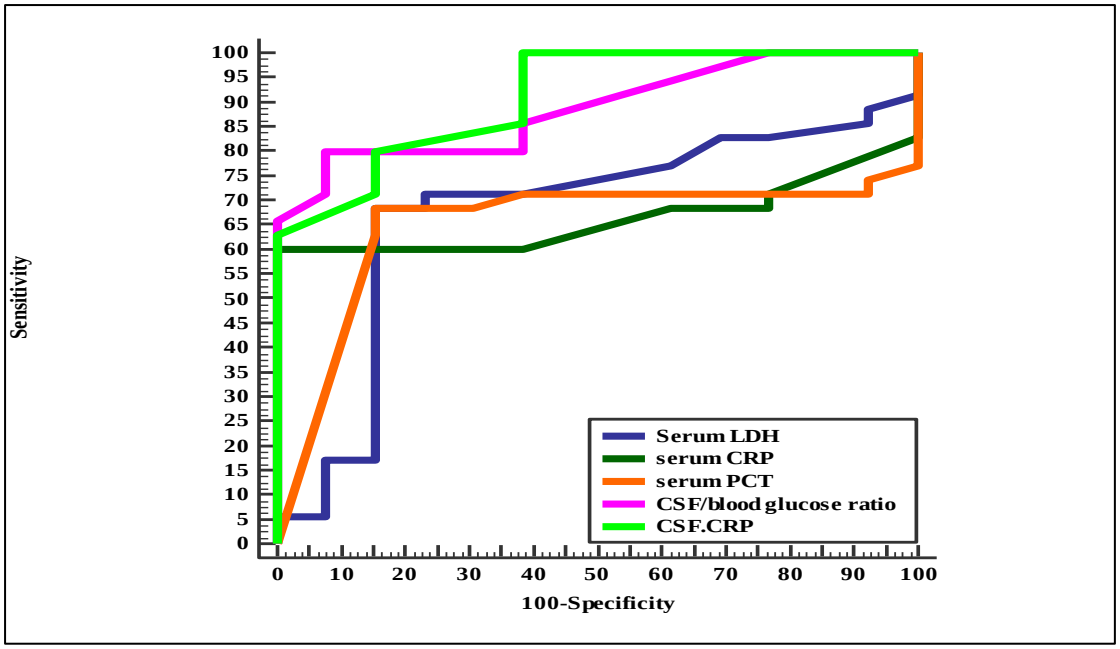

Figure 1: ROC curve shows Accuracy of serum and CSF biomarkers in differentiation between bacterial and viral meningitis.

It was found that multiplex PCR had 94% sensitivity and 100% specificity for diagnosis of bacterial meningitis versus viral meningitis with overall accuracy was 95.6% and area under curve was 0.94.

Discussion

Bacterial meningitis remains a significant global health concern, particularly among pediatric populations. Its incidence differs across regions, age groups, and pathogens involved. In developing nations, the prevalence ranges from 0.07% to 2.5% among children under five years old. It is a critical condition associated with considerable morbidity and mortality in children **(5).**

Consistent with the present study, **Chauhary et al., 2017** evaluated 60 children suspected of having meningitis, with the majority being males (61.67%) and aged between 2 to 5 years (52%). Similarly, **Yadhav Ml (2014)** studied 50 children with a mean age of 3.56 years, with most of the cases being two years old **(6, 7).**

In our current study, all enrolled patients exhibited fever and signs of meningeal irritation. A disturbed level of consciousness was noted in 43 patients (89.6%), and convulsions occurred in 38 patients (79.2%). Additionally, signs of increased intracranial pressure were observed in 8 cases (16.7%). It is well recognized that infants as young as three months may exhibit neurological symptoms such as irritability, lethargy, or behavioral changes. On the other hand, children older than two to three years usually exhibit fever associated with indications of increased intracranial pressure, such as headache and meningeal signs **(8).**

However, **Dashti et al., 2017** found that vomiting (72%), poor feeding/loss of appetite (74%), convulsions (44%), and meningeal symptoms (34%), were the most frequent clinical manifestations among their group. The younger age group (less than a year) that was included in their study may be the cause of this disparity **(9).**

In our study, bacterial meningitis was more frequently diagnosed than viral meningitis in developing countries. This could be attributed to socio-economic challenges such as poor hygiene, substandard housing, lack of sanitation, and the inappropriate use of antibiotics, which collectively promote the spread of infection and emergence of resistant bacterial strains **(1, 10).**

Furthermore, bacterial pathogens continuously evolve, developing resistance to conventional antibiotics. This resistance often results from improper antimicrobial use, leading to strains capable of evading both pharmacological treatments and immune responses **(11)**.

Although CSF analysis and culture remain the gold standard for diagnosing bacterial meningitis, these methods are time-consuming and have moderate sensitivity (70–85%). Prior antibiotic use and technical factors may reduce culture yield, making rapid decision-making challenges **(9, 12)**.

Based on clinical criteria and CSF culture results, 20 of the 32 positive cases were diagnosed with bacterial meningitis (62.5%), and 12 (37.5%) with viral meningitis. Positive CSF cultures were found in only 20 cases (41.7%), while 28 cases (56.3%) showed no bacterial growth. These findings support earlier reports on the limited diagnostic yield of CSF cultures, which ranges from 6.9% to 80% **(5, 9, 12, 13).**

In agreement with our results, **Chaudhary et al., 2017** reported that bacterial meningitis was more prevalent (75%) compared to viral meningitis (13%), while 12% of their patients had febrile seizures **(6).**

The multiplex PCR by BIOFIRE FILMARRAY system in our study successfully detected viral agents in cases suspected of viral meningitis (6 enterovirus and 6 herpes simplex virus) but failed to detect pathogens like Klebsiella pneumoniae and Staphylococcus aureus, which were not included in its detection panel. However, this multiplex PCR method demonstrated no cross-reactivity with unrelated bacterial species or fungi and was straightforward, extremely sensitive, and specific. By identifying bacterial DNA in culture-negative CSF samples in less than three hours, it performed better than conventional cultures **(14).**

Our results showed that the multiplex PCR had a 94% sensitivity and 100% specificity for bacterial meningitis diagnosis, with an area under the curve (AUC) of 0.94 and a diagnostic accuracy of 95.6% overall. With a sensitivity of 87–100% and a specificity of 98–100%, this technique can also identify infections in blood or CSF even after antibiotics have been administered **(14, 15, 16, 17).**

Procalcitonin and CRP are commonly used biomarkers that frequently surpass absolute neutrophil count (ANC) and leucocytes count in detecting severe bacterial infections in children. Interestingly, procalcitonin is particularly helpful in identifying meningococcal disease and other invasive bacterial infections **(18).**

In comparsion of bacterial with viral meningitis, the current study revealed that patients with bacterial meningitis had significantly higher serum CRP (91.26 ± 46.10 ng/dL vs 19.72 ± 14.47 ng/dL; $P < 0.05$), in comparison to those with viral meningitis. Also, mean age of patients with viral meningitis was significantly lower than those with bacterial meningitis (2.65 ± 1.06 vs. 3.50 ± 1.28 (years); P= 0.03). In line with the current study, a previous study revealed that patients with bacterial meningitis had signficnatly higher serum CRP in comparison to those with viral meningitis, but this study disagreed with the current with insignficnat difference between both groups as regard mean age of patients **(13).**

To differentiate between bacterial and viral meningitis, we evaluated the diagnostic efficacy of serum CRP, PCT, LDH, CSF-CRP, and the CSF/blood glucose ratio. Serum CRP demonstrated 60%

sensitivity and 100% specificity (accuracy: 70.8%) at a threshold of >29.9 mg/dL. This supports CRP's usefulness as a discriminative marker and is consistent with other research that found its sensitivity and specificity to be between 70–100% and 90–95%, respectively, at cutoff values over 57 mg/dL **(9).**

For serum PCT, at a cutoff >0.23 ng/dL, sensitivity was 69%, specificity was 85%, with an overall accuracy of 73.3% (AUC = 0.67). Similarly, **Dashti et al., 2017** found a sensitivity of 66.7% and specificity of 59.3% at a cutoff >6 ng/dL. sensitivity was 69%, specificity was 85%, with an overall accuracy of 73.3% (AUC = 0.67). Similarly, **Dashti et al., 2017** found a sensitivity of 66.7% and specificity of 59.3% at a cutoff >6 ng/dL **(9).**

Serum LDH levels were considerably higher in patients with bacterial meningitis than in those with viral meningitis (232.65 ± 57.09 vs. 123.30 ± 19.71 U/L; P = 0.04). Sensitivity and specificity were 69% and 85%, respectively, with 73% accuracy (AUC = 0.67) at a threshold >205 U/L. More research is still needed to determine serum LDH's diagnostic utility.

CSF-CRP showed the best diagnosis accuracy of any biomarker. Sensitivity was 80%, specificity was 92.3%, accuracy was 82.3%, and AUC was 0.91 at a threshold >0.18 mg/dL. **Attia et al., 2020** established a CSF-CRP threshold of ≥5.25 mg/L, which produced 100% sensitivity, 95% specificity, and 98% overall accuracy (AUC = 0.999), supporting these findings **(19).** Last but not least, the CSF/blood glucose ratio achieved 84% specificity and 80% sensitivity at a threshold of less than 0.33 (accuracy: 81.1%; AUC = 0.89). This aligns with **Tamune et al., 2014**, who reported sensitivity and specificity of 92.9% at a cutoff of point **(20).**

Conclusion

Differentiation between bacterial and viral meningitis is a great point of challenge in the clinical practice where the main therapy of viral meningitis is usually supportive while the bacterial meningitis requires intense course of antibiotics as early as possible. Till now, culture of the CSF remains the main gold standard test for differentiation and diagnosis of bacterial meningitis. But it usually has low diagnostic yield and time consuming. So many available biomarkers and methods used to overcome these drawbacks. One of them are multiplex PCR that was proven to have the best diagnostic accuracy for early diagnosis and differentiation of

meningitis than CRP- CSF, CSF/blood glucose ratio and serum PCT in order of research results.

Declaration of conflicting interests

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Ethical approval

The study was approved by the Ethics committee of Assiut Faculty of medicine (IRB No.17100640).

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