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Review Article
Diagnostic Performance of Interleukin-6 for Bacterial Meningitis: A Review

[1]Ibrahim Dan Dano, [1]Sani Ousmane and [2]Hassimi Sadou

[1]Centre de Recherche Médicale et Sanitaire (CERMES), 634 Boulevard de la Nation YN034, BP: 10887, Niamey, Niger
[2]Université Abdou Moumouni, Faculté des Sciences et Techniques, BP: 10662, Niamey, Niger

Abstract
Many studies have investigated the potential of using cerebrospinal fluid (CSF) interleukin-6 levels for the diagnosis of meningitis, but they have often provided contradictory results. This critical scientific literature review summarizes various methods used for the diagnosis of bacterial meningitis, including IL-6 assays and the diagnostic power of CSF IL-6 as a biomarker of bacterial meningitis, between 2000 and 2016. An analysis of data from 9 studies involving 292 patients with bacterial meningitis revealed that sample sizes of patients with bacterial meningitis ranged from 9-85. Molecular methods were used to diagnose bacterial meningitis in only one of these studies. Enzyme-linked immunosorbent assays (ELISA) were used in 5 of these studies to determine CSF IL-6 levels. The reported area-under the curve (AUC) varied from 0.660-0.988 and in 6 out of 8 (75%) studies it was $\geq$0.937. The CSFIL-6 cut-off values for the diagnosis of bacterial meningitis ranged from 90 pg dL^{-1} to 51.6 ng mL^{-1} and the sensitivity and specificity of the assays ranged from 61.9-100 and 51-100%, respectively. Different methods were used to determine CSF IL-6 levels and the identification of bacterial meningitis was mostly based on culture without an associated molecular method. There is a need to standardize methods to ensure accurate diagnoses. Further studies that recruit a large number of patients with bacterial meningitis are required to validate these findings.

Key words: Interleukin-6, cerebrospinal fluid, diagnostic performance, bacterial meningitis, ELISA

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Corresponding Author: Ibrahim Dan Dano, Centre de Recherche Médicale et Sanitaire (CERMES), 634 Boulevard de la Nation YN034, BP: 10887, Niamey, Niger Tel: +227 20 75 20 40 Fax: +227 20 75 31 80

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Meningitis is an inflammation of the protective membranes (meninges) and/or cerebrospinal fluid (CSF) that surround and protect the brain and spinal cord. Meningitis has many causes, both infectious and non-infectious. Bacterial meningitis (BM), mainly caused by *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenza*, has high morbidity and mortality rates and requires prompt recognition, early diagnosis and rapid treatment[1]. Aseptic meningitis (AM) is mainly caused by viruses, such as enterovirus, arbovirus and herpes simplex virus and is often less severe[2,3]. Many studies have evaluated new as well as classical markers for meningitis in order to develop optimal tests for the fast diagnosis of bacterial meningitis that can distinguish acute bacterial meningitis from aseptic meningitis upon patient admission[4]. New biomarkers for inflammation include cytokines such as tumour necrosis factor TNF-α, interleukin IL-1β, IL-6 and IL-8. Many studies suggest that cytokines that are involved in immune responses and modulation of inflammation are potential markers for meningeal inflammation[5]. There may be a correlation between cytokine concentrations in cerebrospinal fluid (CSF) and morbidity and mortality rates[6]. According to many studies, IL-6 plays a valuable role in the diagnosis of bacterial meningitis[7]. This study aims to describe the performance of IL-6 measurements in the diagnosis of bacterial meningitis reported between 2000 and 2016.

A systematic scientific literature review was performed using the keywords "Interleukin-6", "Bacterial meningitis", "Cerebrospinal fluid", "Diagnosis" alone and in various combinations. Searches were carried out in electronic databases such as PubMed, HINARI and Google Scholar. Only studies that reported the area under the curve (AUC) or the specificity and sensitivity for the diagnostic power of IL-6 were considered (Table 1).

Analysis of selected studies

Study characteristics report: After a systematic review and selection, a total of 9 studies conducted across four continents were included for the present analysis[4,8-15]. Four (44.5%) of these studies were done in Asia, 2 (22.2%) in Europe and 2 (22.2%) in America. Only 1 study (11.1%) was done in Africa. Three studies involved samples from children aged ≤15 years and 3 others involved samples from adults aged ≥18 years. The remaining studies included patients from all age groups. A total of 292 patients with bacterial meningitis were included in these studies. The sample size per study ranged between 9

Table 1: Diagnostic power of CSF IL-6 levels for BM diagnosis obtained from studies performed during 2000-2016

		Sample size								
Country	Age (years)	BM	AM	Dates of sample collection	Assay method	AUROC (95%CI)	Cut-off value	Sensitivity (%)	Specificity (%)	References
Niger	≤15	85	35	February, April, 2015	ELISA	0.94 (0.901-0.979)	1,065.96 pg mL^{-1}	76.2	100	Dano *et al.*[8]
Spain	0-88	41[a]	65	January, 2008-June, 2009 and February-November, 2013	ECLIA	0.937 (0.985-0.978)	1,418 pg mL^{-1}	95.5	77.5	Garcia-Hernandez *et al.*[9]
Japan	18 -77	13	21	April, 2008-August, 2012	CLEIA	0.962 (0.922-1.003)	644 pg mL^{-1}	92.3	89.5	Takahashi *et al.*[10]
India	≤14	57	15	January, 2010-April, 2012	ELISA	0.974 (0.87-1)	100 pg mL^{-1}	96	100	Prasad *et al.*[11]
Argentina	18-87	13	27	May-October, 2009	ELISA	Not available	90 pg dL^{-1}	100	95	Vazquez *et al.*[12]
China	≤75	22	40[b]	January-December, 2011	RI	0.830 (0.693-0.967)	51.6 ng mL^{-1}	61.9	95.1	Chen *et al.*[13]
Brazil	BM: 0.2-50, AM: 0.5-46	9	18	AM: 2005, BM: 2007	ELISA	0.660 (0.444 - 0.876)	Not available	Not available	Not available	Pinto *et al.*[14]
China	1-15	12	41	January, 1999-January, 2003	ELISA	Not available	Not available	96	51	Hsieh *et al.*[15]
Germany	BM: 38.8-64.2, AM: 29.0-62.3[c]	40	46	Retrospective study	SPSCI	0.988	2,500 ng L^{-1}	93	93.1	Kleine *et al.*[4]

[a]26 patients with BM confirmed by positive culture and 15 patients with negative culture, or not performed, [b]10 patients with tuberculosis and 30 patients with viral meningitis, [c] Range; CLEIA: Chemiluminescent enzyme immunoassay, ELISA: Enzyme-linked immunosorbent assay; SPSCI: Solid-phase sandwich chemiluminescent immunoassay, RI: Radio immunoassay, ECLIA: Electro- chemiluminescent immunoassay; AUROC: Area under the receiver operating characteristic curve

and 85 patients with bacterial meningitis. The study with the highest number of patients with bacterial meningitis was conducted in a Sub-Saharan African country. In 4/9 (44.5%) studies, the number of patients with bacterial meningitis was ≤13 patients.

Diagnostic methods for bacterial meningitis: In all selected studies, the diagnosis of bacterial meningitis was based on clinical signs and biological methods. The main biological methods for bacterial meningitis diagnosis included cytological analyses (9/9 studies)[4,8-15], gram stain of CSF (9/9 studies)[4,8-15], CSF glucose and protein analysis (8/9 studies)[4,8-14] and culture methods (9/9 studies)[4,8-15]. Molecular methods were used for the diagnosis of bacterial meningitis in only one study[8]. In 2 studies, CSF antigen tests were also performed[10,15]. In 5/9 studies, ELISA methods were used to determine CSF IL-6 levels[8,11,12,14,15].

CSF IL-6 assay methods: Enzyme-linked immunosorbent assays (ELISA) were used in 5/9 studies to determine CSF IL-6 levels. Other methods used include chemiluminescent enzyme immunoassays (CLEIA), solid-phase sandwich chemiluminescent Immunoassays (SPSCI), Radio immunoassays (RI) and electro chemiluminescent immunoassays (ECLIA).

Diagnostic accuracy of CSF IL-6: Bacterial meningitis is a medical emergency requiring immediate attention. The diagnosis of BM relies mainly on the isolation of bacteria from CSF samples. However, in 70% of clinically suspected cases, bacterial CSF cultures remain negative[16]. Clinical guidelines recommend initiating empirical antibiotic therapy in suspected cases of BM, despite the risk of microbial antibiotic resistance[9]. Other diagnostic methods for BM include clinical examination and biological tests such as CSF cytology and CSF glucose and protein levels[17]. Other biomarkers in CSF, including cytokines, have been explored in order to increase the number of available biological indicators that are informative about inflammation intensity in the subarachnoid space[18]. Cytokines are molecules involved in the modulation of immune and inflammatory processes. The IL-6 is a cytokine involved in both innate and adaptive immunity and exerts diverse actions. The main cellular action of IL-6 is to stimulate the growth of B lymphocytes that have differentiated into antibody-producing cells[14]. Many studies have revealed the role of IL-6 in BM pathogenesis and a meta-analysis by Yao *et al.*[7], who also reported that IL-6 can play a valuable role in diagnosing bacterial meningitis, but a specific profile of IL-6 for BM diagnosis is not yet available.

Most of the studies identified and analysed in this review reported that IL-6 is a better marker for diagnosis of BM than other routine CFS markers. An AUROC value ≥0.937 for 6 out of 8 (75%) studies indicates that IL-6 is a good biomarker for BM diagnosis. Furthermore, the high estimated sensitivity (≥92.3%) in 75% of the studies, as well as the high estimated specificity (≥93.1%) in 62.5% of the studies, indicate a low rate of missed diagnosis (7.7%) and misdiagnosis (6.9%), respectively. A meta-analysis based on 9 studies carried out between 1995 and 2014 found a pooled sensitivity of 91% and specificity of 93%[7].

In two studies[13,14], the AUROC reveals a poor diagnostic value. The BM group of one of these two studies was composed of cases confirmed by culture; patients were treated with steroid and/or antibiotics and pleocytosis was observed, with >50% neutrophils[13]. Pre-treatment with antibiotics or steroids is a limitation to this study. High CSF IL-6 levels comparable to BM have been reported in AM with pleocytosis, including neutrophilia or lymphocytosis[8]. There is a significant correlation between IL-6 concentration and the severity of the patient's clinical condition on admission[19] and during the subsequent course of disease. According to Kepa *et al.*[18] in cases where patients recovered from the disease, IL-6 concentrations were reduced. In the majority of cases, this preceded clinical improvement and normalization of other CSF parameters. In a second study[14], the concentrations of IL-6 obtained were similar between AM and BM, showing little utility in differentiating AM from BM. However, the number of patients included in this study was very low. It is important to note that different cut-off values of CSF IL-6 levels were obtained depending on the method or type of reagent used. The lowest IL-6 cut-off value was obtained by Vazquez *et al.*[12], who obtained globally lower values of IL-6 in their population study. The second study that reported low cut-off values of IL-6 was that of Prasad *et al.*[11]. About half of BM patients included in this study (29/57) had a history of antibiotic use (3rd generation cephalosporin) as recently as 72 h before IL-6 levels were measured. However, despite the lower values of IL-6 obtained in these studies, significant differences were observed between BM and AM.

In 8 out of 9 studies, the diagnosis of BM was based on culture, leukocyte count and CSF protein and glucose levels. However, many studies[18,20-22] have shown that CSF culture is an imperfect standard for the diagnosisof BM. Studies show that CSF culture is positive in 70-95%[18,20] of patients diagnosed with BM who have no history of prior antibiotic therapy. Another study showed that CSF culture had an extremely high specificity (close to 100%) but low sensitivity (approximately 50%)[22]. The isolation of meningococci from biological samples

remains delicate because of the low viability of bacteria and the need for constrained transport and conservation conditions[23]. Another factor is that early antibiotic therapy is increasingly recommended in cases of suspected meningococcal disease, even before CSF collection. This makes isolation of the bacteria even more difficult and the rate of isolation of meningococci decreases by up to 50%, when the patient has been previously treated with antibiotics[9]. Another limitation of culture is that it is time-consuming. Gram staining of CSF reveals the presence of bacteria in 50-80% of cases[9], but the absence of bacteria does not exclude bacterial meningitis, particularly if antibiotics were administered before the sample was taken[13]. Molecular methods are necessary for the diagnosis of BM and can be used even in cases of antibiotic therapy and at early stages of the disease. However, culture is essential for the identification of antibiotic sensitivity. Molecular methods, when associated with culture and other CSF parameters (CSF gram stain, leukocyte count, CSF protein and glucose), can allow differential identification of BM prior to and during antibiotic therapy as well as improve the sensitivity and specificity of the diagnosis. The small number of BM cases, the diagnostic criteria of BM and wide age ranges are the limitations found in some studies[9]. Most of these studies were performed outside of the meningitis belt, the most affected geographical zone[8]. For over 100 years, large meningococcal meningitis outbreaks have occurred periodically in the African meningitis belt[24,25]. Only one study was done in this area and it occurred during a meningitis epidemic[26], therefore, it reported the highest numbers of BM patients. During the acute phase of meningitis, distinguishing BM from AM is not easy for clinicians since the symptoms are often similar. Therefore, rapid diagnostic laboratory tests that permit differential diagnoses of meningitis are needed. If a test can allow for evaluation of disease severity, it provides an advantage that could improve the management of meningitis by identifying patients with a high risk of death who require intensive care.

CONCLUSION

The IL-6 is a potential biomarker for the diagnosis of bacterial meningitis. Different methods were used to determine CSF IL-6 levels and the identification of bacterial meningitis was mostly based on culture without an associated molecular method. There is a need to standardize methods in order to ensure accuracy. Molecular methods can improve diagnostic methods by increasing sensitivity. Further studies that recruit a large number of patients with bacterial meningitis are required in order to best validate findings for future practice in emergency laboratories.

SIGNIFICANCE STATEMENT

This study shows the potential role of cerebrospinal fluid level of interleukin-6 as a biomarker for cerebrospinal fluid inflammation during meningitis and its benefit for diagnosis of bacterial meningitis. This study helps researchers by describing the diagnostic power of the potential role for CSF IL-6 in bacterial meningitis diagnosis and the limitations of some studies in order to improve future studies. Thus, molecular methods can improve the diagnosis of bacterial meningitis by improving sensitivity and allowing better interpretation of results.

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