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Review Article

Cerebrospinal Fluid Cytokines in Diagnosis of Acute Bacterial Meningitis

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Abstract

Acute bacterial meningitis in children is associated with high mortality and morbidity in developing countries including India due to poor immunization coverage, delayed diagnosis and lack of appropriate treatment. Although Cerebrospinal Fluid (CSF) microscopic and routine examination has been used as a tool to diagnose bacterial meningitis, it has poor sensitivity and specificity. Detection of cytokines such as TNF α, IL-6 and IL-8 in the CSF has been suggested for early diagnosis and differentiation of various etiological subgroups of meningitis. This review aims to summarize the diagnostic performance of these cytokines for the same in various studies in existing literature.

Keywords: Meningitis; Tumour Necrosis Factor (TNF-α); Interleukin-6(IL-6); IL-8

Introduction

Acute Bacterial Meningitis is a life threatening condition associated with high mortality and morbidity. Although bacterial meningitis account for only minority (approximately 5%) of the total cases, it is the most severe form and associated with mortality ranging from 2% in infants and children to as high as 30% in neonates and adults [1,2]. The case fatality rates are even worse in developing countries with various reported mortality rates of 37 to 60% despite use of appropriate therapeutic and diagnostic advancements in contrast to the developed nations. The difference in mortality can be attributed to poor immunization coverage, delayed diagnosis and lack of appropriate treatment in developing countries. Patients who survive, 1/3rd are left with various neurological sequelae such as deafness, blindness, motor deficit or cognitive impairment [3].

The diagnosis of bacterial meningitis although primarily relies upon CSF examination [4], has poor sensitivity and specificity in differentiating the etiological subgroups [5], Clinical assessment, cytology, CSF culture, Gram's staining, biochemical test and newer tests such as CSF CRP, serum procalcitonin, CSF cytokines and CSF PCR have been used to diagnose and differentiate bacterial from non-bacterial causes of meningitis. As none of these tests is unequivocally optimal, empirical use of antibiotics have resulted in unnecessary hospitalization and increased cost [4-6].

Cytokines in Diagnosis

Cytokines (mainly TNF α, IL6 and IL8), chemokines, proteolytic enzymes, and oxidants play an important role in inflammatory cascade and brain dysfunction associated with bacterial meningitis [7]. Tumor necrosis factor-alpha (TNF-α) is a potent activator of neutrophils and mediates adherence, chemo taxis, degranulation, and the respiratory burst. Interleukin-6 (IL-6) stimulates the growth of B lymphocytes that have differentiated into antibody producing cells. Interleukin-8 (IL-8) acts as a chemo attractant for neutrophils to the site of inflammation. IL-6-deficiency has been shown to result in higher CNS bacterial colonization and lower survival in murine model [8]. A higher concentration of TNF-α, IL-6 and IL-8 in patients with bacterial meningitis has been reported in various studies and has been successfully used in early diagnosis as well as differentiating bacterial and viral meningitis [9]. Various studies have found them to be the most sensitive and specific inflammatory markers of bacterial meningitis [10,11].

Literature Review on Cytokines

Cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-8, and IL-6 are expressed in the CNS after local bacteria inoculation and are detectable up to 96 hours [12,13]. The elevated levels of these cytokines in the CSF, implies their role in the pathogenesis of bacterial meningitis and can be used in diagnosis and monitoring the treatment response. No association of these cytokines has been reported with the subsequent development of neurological sequelae. Studies have indicated that elevated levels of these cytokines may not be evident in the serum, as their expression may be a local and compartmentalized phenomenon [14].

A significant increase in CSF cytokines levels in the cases of meningitis has been demonstrated in many studies, adding to the diagnostic potential of their analysis.12-14 Most significant of these cytokines are TNF-α, IL-6 and IL-8 [15,16]. Although there are few studies that failed to reveal a statistically significant difference in IL-6 levels between meningitis and non- meningitis groups, but the substantial evidence suggesting significant association cannot be neglected [17,18]. It should be noted that there have been studies reporting elevation of CSF IL-6 in patients of traumatic brain injuries as well, however can easily excluded by a careful clinical history [19]. The elevated cytokines levels can be used to differentiate between bacterial, viral and tubercular etiology as studies have shown higher levels of cytokine (TNF- α, IL-6 and IL-8) in acute bacterial meningitis compared to others [20,21]. These studies have revealed sensitivity and specificity approaching 100%, making this test highly valuable [22-24].

Few studies that assessed each cytokine level individually, failed

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Table 1: Various studies validating usefulness of TNF-α, IL-6 and IL-8 in establishing etiology of Meningitis in children.

Study	Year	Sample size (Bacterial Meningitis)	Sample size (Non Bacterial Meningitis)	Assay Method	Cut off value	Sensitivity (%)	Specificity (%)
TNF α							
Nadal D et al [28]	1989	18	31	ELISA	500 pg/ml	NA	NA
Glimâker M et al [29]	1993	51	78				
Tang RB et al [11]	2001	23	26			74	81
Mukai AO et al [15]	2006	6	13	ELISA			
Prasad R et al [20]	2014	57	30	ELISA	500 pg/ml	100	100
IL-6							
Dulkerian SJ et al [30]	1995	20	42	ELISA	NA	100	79
Hashim IA et al [31]	1995	123	123	Radioimmunoassay	3.4 ng/ml	93	95
Kleine TO et al [32]	2003	40	46	SPSCI	2500 ng/ml	92	93
Hsieh CC et al [24]	2009	12	41	ELISA	10 pg/ml	92	51
Chen Z et al [33]	2012	22	61	Radioimmunoassay	51.6 ng/ml	64	95
Vázquez JA et al [26]	2012	13	27	ELISA	90 pg/ml	92	100
Takahashi W et al [22]	2014	13	57	CLEIA	644 pg/ml	92	89
Prasad R et al [20]	2014	57	30	ELISA	100 pg/ml	96	100
IL-8							
Ostergaard C et al [34]	1996	31	13	ELISA	3µg/L	81	92
Kleine TO et al [32]	2003	40	46	SPSCI	4000 ng/L	48	91
Pinto Junior VL et al [35]	2011	9	18	ELISA	1.685 ng/dl	100	94
Chen Z [33]	2012	22	61	Radioimmunoassay	1.14 pg/ml	91	67
Prasad R et al [20]	2014	57	30	ELISA	75 pg/ml	100	100
Abdelmoez AT et al [23]	2014	40	40	ELISA	3.6 ng/ml	83	85

to demonstrate a significant differences between septic and aseptic meningitis [17,19,25] As there is a positive significant association between different cytokines14, a battery of tests consisting of TNF- α, IL-6 and IL-8 can be done to alleviate any confusion or false negative results. There is no evidence of any association between cytokines and routinely measured CSF parameters [14,21]. These tests can also be performed to differentiate between lymphocytic predominant meningitis and partially treated septic meningitis with high sensitivity and specificity [22], however no significant association has been found between meningitis causing bacterial species and CSF cytokine values (Table 1).

Prognostic Significance

IL-6 levels in CSF has been shown to be directly proportional to the severity of illness but no significant association was found between IL-8 and disease severity [14,21]. The literature also reports a decline in CSF cytokines IL-6, IL-8 and TNF-α levels on serial measurements after initiation of treatment closely correlated with the clinical improvement of the corresponding patients [14,19,21]. In the subgroup of patents not responsive to treatment, the cytokines levels failed to decrease during the serial measurements, and was associated with higher mortality and poorer prognosis [21,26,27]. These findings suggest a role of serial CSF cytokine measurement in monitoring the clinical outcome and treatment of meningitis [19,28-35].

Conclusion

Cytokine estimation is a fast, easy, and reliable test which can be used to differentiate between the etiological factors, monitor treatment and prognosticate the therapeutic outcome in cases of meningitis. However, higher cost, non standardization of the cut-off values and decreased level of awareness limits its routine application in daily clinical practice in the developing countries. Moreover, the standardization of the cutoff value of these tests is required before widespread implementation.

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