Original Research Article

Role of Leukocyte Esterase Levels in Pyogenic Meningitis

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Abstract

Introduction: Meningitis is a medical emergency which requires immediate diagnosis and treatment, delay in diagnosis may results in delay in treatment which can cause neurological deficit with functional impairment or may even death. Unfortunately, bacterial meningitis is more common in developing countries, where there are no laboratory facilities in major primary/ rural health care unit. Hence there is a requirement for cheap, rapid and easily available diagnostic tool to diagnose pyogenic meningitis. Urine dip stick detects pus cells based on leukocyte esterase released by leukocytes, based on that principle the study aims to detect the role of urine dipstick in detecting neutrophils in CSF which is a marker for pyogenic meningitis. **Objectives**: To study the sensitivity, specificity, positive and negative predictive value of leukocyte esterase in pyogenic meningitis. **Methods:** 83 CSF sample of patients with bacterial, viral meningitis and patient with metabolic encephalopathy and other illness (for control) has been analyzed with leukocyte esterase, semi quantitatively by using SD 10 urine dip stick and compared with cell type and cell counts which are detected by conventional methods, and also compared with clinical data retrospectively to avoid observer bias. **Results:** The diagnostic accuracy of the test is good when then cutoff is increased to 100cells/cumm. The diagnostic accuracy for protein strip is fair with k=0.079 and diagnostic accuracy can be improved if the strip is designed specific for CSF analysis. The diagnostic accuracy of glucose is poor because cutoff for the reagent strip is more than 100 and cut off for bacterial meningitis is less than 40 cells/cumm. **Conclusion:** Urine dipstick is useful in detecting pyogenic meningitis in resource poor settings. However it cannot replace conventional cytological, biochemical and microbiological analysis in accurately diagnosing the type of meningitis.

Key words: Pyogenic Meningitis, CSF- Cerebro Spinal Fluid, Leukocyte Esterase.

Introduction

Meningitis is a medical emergency as it involves vicinity of brain and spinal cord, carries high mortality and morbidity. Management of meningitis requires fast and accurate diagnosis and initiation of treatment, delay in management could be lethal and can cause permanent neurological deficit. Diagnosis of meningitis requires laboratory examination of samples of cerebrospinal fluid (CSF) for leukocytes, protein, glucose and culture[1].

Bacterial meningitis can result in spectrum of complications including both neurological and systemic. Neurologic complications include cerebral edema, hydrocephalus, brain abscess, subdural empyema or subdural effusion, cerebrovascular event. Systemic complications include sepsis, septic shock, disseminated intravascular coagulation, reactive arthrirtis, and adult respiratory distress syndrome. These complications are more common when management of meningitis get delayed[2].

The case fatality rate associated with bacterial meningitis prior to antibiotic era (1940) was exceeding 70%, however with invent of antibiotics the rate has come down less than 25%[3].

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Pyogenic meningitis is 10 times more common in low income settings where laboratory facilities often unavailable or inadequate than in well resourced centres[4]. Even in the centers where facilities available the amount of time taken to reach the diagnosis of meningitis using standard technique is an important factor which can results in delay in treatment of meningitis[5]. Hence a simple, cost effective, easily available and rapidly detectable test is required in diagnosis in resource limited area which can decrease morbidity and mortality associated with pyogenic meningitis.Few studies have documented the role of urine dipstick in diagnosing pyogenic meningitis by reagents for detecting leukocyte esterase[1,4-7]. However this technique is not widely practiced clinically, this study tries to reassess the role of urine dip stick in pyogenic meningitis by using SD 10 urine reagent strip.

Objectives

To find the diagnostic accuracy of urinary reagent strip to determine Cerebro spinal fluid biochemical analysis and cytological analysis.

Materials and methods

The Present Cross sectional study was conducted in JSS Medical College, Mysore from 2015 to 2016 for a period of two years .

A total of 83 Samples who met the inclusion criteria were included in the study and analyzed.

Inclusion criteria

All CSF samples which was sent for biochemical and pathological study.

Exclusion criteria

Samples more than 12 hours if not refrigerated, grossly hemorrhagic sample by naked eye examination.

All CSF samples which were sent for biochemical and cytological examination was studied excluding Samples more than 12 hours if not refrigerated, grossly hemorrhagic sample by naked eye examination.

All CSF samples were evaluated in a blinded fashion by first analyzing CSF by SD-10 Urinary reagent strip as an index test, then values of CSF microscopy and biochemical analysis were noted as reference standards, then patient's demographic and clinical diagnosis were noted to avoid bias.

Reference standards

The study compared index test (reagent test) with standard cell types and cell counts by microscopy and also compared with conventional Biochemical test for glucose and protein.

Cell counts, glucose and proteins

Parameters	Adults	Term infants	Preterm infants
Cell count	<5	<32	<29
% PMNS	0	61	57
Protein	9-58	20-170	65-150
Glucose	45-80	34-119	24-63
CSF blood glucose ratio	0.5-0.8	0.44-2.48	0.55-1.55

Results

A total of 83 Study subjects were analyzed in the present study. The age group in our study varied from newborns to geriatrics age group covering subjects in all the age groups. Few of the subjects age was missing due to system error. Majority of the subjects were Male (53%) and Female (47%) in the present study.

The Sensitivity of leukocyte esterase + and above compared with cuttoff of 100 cell/mm^3 is 100%, specificity is 89.3%, positive predictive value of 50% and negative predictive value of 90%.

Specificity and sensitivity can be improved if ++ of dip stick is compared with cutt off value of 100.

The Sensitivity of leukocyte esterase ++ and above compared with cuttoff of 100 cell/mm^3 is 100%, specificity is 98%, positive predictive value of 90% and negative predictive value of 100%.

Sensitivity of protein dip stick with ++ cutoff comparing with 30-100 mg/dl is 46%, specificity and positive predictive value is 100%, negative predictive value is 34%.

However, in most of the bacterial meningitis CSF protein is in the range of > 200 mg/dl.[19] Hence another analysis was done using cut off as +++ and protein value of 100-300 mg/dl showing sensitivity of 17%, specificity and positive predictive value of 100%, negative predictive value of 25%.

Analysis of single parameter of protein dip stick with conventional biochemistry gives poor diagnostic accurary, however combing ++,+++ with biochemical values gives fair agreement in diagnostic accuracy with kappa value of 0.079.

Since in pyogenic meningitis CSF glucose are usually less than 40mg/dl[19], but the urine dip stick can detect only glucose levels are more than 100mg/dl, test could not be interpreted.

Statistical analysis shows urine dip stick has poor diagnostic value in detecting RBCs, if individual parameters are taken. However, combing ++ and +++ yields fair strength of agreement with SE of kappa 0.074.

Table 1: Socio Demographic Features of the study

		Frequency	%
Age Group	**<10 Years**	7	9.6
	11-20	3	4.1
	21-30	14	19.2
	31-40	17	23.3
	41-50	6	8.2
	51-60	13	17.8
	61-70	9	12.3
	>70	4	5.5
	Total	73	100
	System missing age	10	
Gender	**female**	39	47
	male	44	53

Table 2: Clinical Diagnosis among the study subjects

	Diagnosis	Valid Percent
Cerebral malaria	1	1.2
cns mets	1	1.2
AIDP	6	7.2
beningn intra cranial hypertension	1	1.2
cryptococcol meningitis	1	1.2
drug induced seizure	1	1.2
metabolic encephalopathy	10	12
multiple sclerosis	1	1.2
Neoplastic	1	1.2
pyogenic meningitis	8	9.6
recurrent pyogenic meningitis	1	1.2
septic encephalopathy	1	1.2
TBM	16	19.3
transverse myelitis	1	1.2
viral menigoencephalitis	33	39.8
Total	83	100

Table 3: Association between Leucocyte Esterase * Neutrophil Count

			Neutrophil Count		Total
			<100	>100	
Leucocyte Esterase	Negative	Count	67	0	67
		% within Leucocyte Esterase	100.0%	0.0%	100.0%
		% within Neutrophil Count	89.3%	0.0%	80.7%
	Positive	Count	8	8	16
		% within Leucocyte Esterase	50.0%	50.0%	100.0%
		% within Neutrophil Count	10.7%	100.0%	19.3%

Table 4: Assessment of semi quantitative accuracy of reagent dip sticks with index test.

			Neutrophil Count			Total
			<25	25-100	>100	
Leucocyte Esterase	-	Count	67	0	0	67
		% within Neutrophil Count	91.8%	0.0%	0.0%	80.7%
	+	Count	5	1	0	6
		% within Neutrophil Count	6.8%	50.0%	0.0%	7.2%
	++	Count	1	0	3	4
		% within Neutrophil Count	1.4%	0.0%	37.5%	4.8%
	+++	Count	0	1	5	6
		% within Neutrophil Count	0.0%	50.0%	62.5%	7.2%

Symmetric Measures					
		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa	.053	.028	3.619	.000

Table 5: Assessment of semi quantitative accuracy of reagent dip sticks with index test (Combining +++ and ++)

Leucocyte Esterase * Neutrophil Count Crosstabulation						
			Neutrophil Count			Total
			<25	25-100	>100	
Leucocyte Esterase	-	Count	67	0	0	67
		% within Neutrophil Count	91.8%	0.0%	0.0%	80.7%
	+	Count	5	1	0	6
		% within Neutrophil Count	6.8%	50.0%	0.0%	7.2%
	++/+++	Count	1	1	8	10
		% within Neutrophil Count	1.4%	50.0%	100.0%	12.0%

Number of observed agreements: 76 (90.48% of the observations)
Number of agreements expected by chance: 59.5 (70.82% of the observations)
Kappa= 0.674
SE of kappa = 0.098
95% confidence interval: From 0.482 to 0.865. The strength of agreement is considered to be 'good'.
The Sensitivity of leukocyte esterase ++ and above compared with cuttoff of 100 cell/mm^3 is 100%, specificity is 98%, positive predictive value of 90% and negative predictive value of 100%.

Table 6: Comparing dip stick protein value with Conventional biochemical protein estimation in CSF

Protein Strip * CSF Protein Cross tabulation						
			CSF Protein			Total
			<30	30-100	100-300	
Protein Strip	-	Count	9	21	1	31
		% within CSF Protein	81.8%	52.5%	3.2%	37.8%
	+	Count	2	16	12	30
		% within CSF Protein	18.2%	40.0%	38.7%	36.6%
	++	Count	0	3	13	16
		% within CSF Protein	0.0%	7.5%	41.9%	19.5%
	+++	Count	0	0	5	5
		% within CSF Protein	0.0%	0.0%	16.1%	6.1%

Poor Agreement

Symmetric Measures					
		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa	-.054	.038	-1.328	.184

Table 7: Comparing dip stick glucose value with Conventional biochemical glucose estimation in CSF

			CSF GLUCOSE			Total
			<100	100-250	>250	
Glucose Strip Value	<100	Count	59	17	1	77
		% within CSF Glucose	96.7%	85.0%	100.0%	93.9%
	100-250	Count	1	0	0	1
		% within CSF Glucose	1.6%	0.0%	0.0%	1.2%
	250-500	Count	1	3	0	4
		% within CSF Glucose	1.6%	15.0%	0.0%	4.9%

Again Poor Agreement Is Seen For Glucose

Symmetric Measures					
		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa	.058	.052	1.153	.249

Table 8: Comparing the detection of RBCs by reagent dip stick with conventional cytological study

			CSF BLOOD			Total
			NIL	FEW	PLENTY	
Blood Strip	-	Count	18	2	0	20
		% within CSF Blood	51.4%	9.5%	0.0%	24.1%
	+	Count	13	4	0	17
		% within CSF Blood	37.1%	19.0%	0.0%	20.5%
	++	Count	1	13	3	17
		% within CSF Blood	2.9%	61.9%	11.1%	20.5%
	+++	Count	3	2	24	29
		% within CSF Blood	8.6%	9.5%	88.9%	34.9%

Poor Agreement

Symmetric Measures					
		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa	.104	.053	1.961	.050

Discussion

The study compared index test (reagent leukocyte esterase strip, protein strip, and glucose strip) with standard test (leukocyte estimation by microscopy, protein and glucose estimation with conventional biochemical analysis)

The strength of the study is, it compared diagnostic accuracy of leukocyte esterase with different cutoff and studied the diagnostic accuracy when combing the cutoff than individual cutoff.

The diagnostic accuracy is improved by taking ++ as cutt off compared with 100 cell/cumm. The Sensitivity of leukocyte esterase ++ and above compared with cuttoff of 100 cell/mm^3 is 100%, specificity is 98%, positive predictive value of 90% and negative predictive value of 100%.In a study conducted by joshi et al showed. Leukocyte esterase positivity by test strip had a sensitivity of 85.2 (95% CI 66.3-95.8%) and specificity of 89.6 (95% CI 77.3-96.5%) for detection of CSF granulocytes of more than 10/cumm[5].Another study conducted in NIMHANS showed the sensitivity and specificity for leucocytes by the strip method for >10 cells/cumm were 96.6% (95% CI: 82.7–99.9%) and 94.5% (95% CI: 86.5–98.4%), respectively[8].Another study by Deloziers and Auerbach showed that Leukocyte esterase have the sensitivity of 73% and specificity of 95% in detecting 10 cells/cumm[31].Using COMBUR 10, COMBUR 9 strips, Parmar *et al* reported the sensitivity and specificity of the reagent strips for the diagnosis of meningitis as 97.14% and 96.42%, respectively. The sensitivity and specificity for tuberculous meningitis and bacterial meningitis were reported as 100% and 96.55%, respectively, and the values for aseptic meningitis as 70% and 96.55%, respectively. Accuracy for the diagnosis of meningitis as a whole, bacterial meningitis, tuberculous meningitis, and aseptic meningitis was reported as 96.78%, 98.2%, 98.27%, and 83.0%, respectively[25].Romanelli *et al.* compared the results of reagent strips and those of the cytological and biochemical assay, and obtained values for sensitivity, specificity, positive and negative predictive values, and accuracy (90.7%, 98.1%, 95.1%, 96.4%, and 96.1%, respectively)[32].Moosa *et al.* and Salvador *et al.* used Combur-9 strips and found this method useful in making a rapid bedside diagnosis of meningitis[26,27].

Previous study had good sensitivity and specificity with cutoff of 10 cells/cumm[5,6,25,26,27,31,32]. Those study was done on combur 10 reagent kit, whereas present study was done by SD 10 reagent kit where the manufcaturer's cuttoff for + LE is 25 cells/cumm though it can detect cells from 10-25 but with very low sensitivity.

Palmer et al also tested the diagnostic accuracy of reagent strip test in Tubercular meningitis[25], though reagent strip can approximately detect PMN s count percentage of PMNs cannot be made out without detecting other cells in CSF.In most of the pyogenic meningitis PMN counts will be more than 1000cells/cumm[19] so cuttoff of 10 cells/cumm is not going to give much information on diagnosing pyogenic eningitis hence this study compared the diagnostic accuracy of reagent strip with cutt off of ++ comapred with 100 cells/cumm, and yeilded 100% sensitivity, 98% specificity, 90% positive predictive value and 100% negative predictive value.

The study also assessed the diagostic acuuracy when combing ++,+++ with CSF PMNs found to have good agreement .

Sensitivity of protein dip stick with ++ cutoff comparing with 30-100 mg/dl is 46%, specificity and positive predictive value is 100%, negative predictive value is 34%.

However, in most of the bacterial meningitis CSF protein is in the range of > 200 mg/dl[19]. Hence another analysis was done using cut off as +++ and protein value of 100-300 mg/dl showing sensitivity of 17%, specificity and positive predictive value of 100%, negative predictive value of 25%.

Analysis of single parameter of protein dip stick with conventional biochemistry gives poor diagnostic accuracy, however combing ++, +++ with biochemical values gives fair agreement in diagnostic accuracy with kappa value of 0.079.Study by Joshi et al showed protein reagent strip positivity had a high sensitivity for detection of CSF proteins greater than 30 mg/dl [98.1 (95% CI 90.1-100%)], the specificity was low [57.1 (95% CI 34-78.2%)] due to a higher proportion of false positives detected with the strip test. Specificity improved when we used a higher cut-off detection of 2 + or higher and CSF proteins (greater than 100 mg/dl). Using tests in combination did not result in higher accuracy estimates[5]. Similar results were found by kumar et al, parmer et al and romaneli et al[6, 25, 32].In the study conducted by Panduranga the results are acceptable for a higher cut-off level of ≥100 mg/dl, where the sensitivity and specificity were 96% and 87.1%, respectively, while at ≥30 mg/dl, the strip was more sensitive and less specific[8].Again the difference in the results of the present study with the previous study is due to different cutoff values provided by manufacturer, however in most of the bacterial meningitis CSF protein will be more than 200 mg/dl hence cutoff of 100 mg/dl yields good results though the present study failed to prove that probably due to number of RBCs in that particular CSF samples.

The present study also assessed the combination of ++ and +++ with routine protein estimation which was found be fair agreement with k=0.079.

Glucose Estimation

In the present study, the reagent strip can detect only when glucose value is more than 100 mg/dl where as previous study used the strip which can detect glucose if more than 50mg/dl[5,6,8,25].

Since in most of pyogenic meningitis have CSF glucose value < 40mg/dl and the reagent kit can detect sugars only if more than 100 mg/dl, and CSF glucose also depends on Serum glucose, serum glucose was not measured and recorded in the study hence glucose estimation is not found to valid, hence it had a poor sensitivity and specificity with poor diagnostic value[19].

Blood Estimation

Though estimation of blood cells are not helpful in pyogenic meningitis, it helps in studying the reliability of other test like protein and leukocyte esterase estimation, for eg high blood cells in the CSF can produce false positive high protein and leukocyte levels, in the present study on false positive leukoctyte esterase ++ when actually there are no PMNs may be due to high RBCs in CSF, so naked eye examination for RBCs and reagent kit examination can give clinical clue whether to consider Leukocyte esterase as false positive or true positive. In the present study statistical analysis shows urine dip stick has poor diagnostic value in detecting RBCs, if individual parameters are taken. However combing ++ and +++ yields fair strength of agreement with SE of kappa 0.074.

Previous study did not reported on RBCs estimation by reagent kit.

Conclusion and recommendation

This study proves urine dip test for detection of leukocyte esterase can be helpful in diagnosing bacterial meningitis which warrants immediate treatment. Though conventional cytological, biochemical microbiological tests are gold standard in diagnosing bacterial and other meningitis this reagent strip test can be used as rapid diagnostic test in resource limited setup. The diagnostic accuracy of the test is good when then cutoff is increased to 100cells/cumm. The diagnostic accuracy for protein strip is fair with k=0.079 and diagnostic accuracy can be improved if the strip is designed specific for CSF analysis. The diagnostic accuracy of glucose is poor because cutoff for the reagent strip is more than 100 and cut off for bacterial meningitis is less than 40 cells/cumm. The specially designed kit targeting CSF analysis with different cutoff than urine dip stick can be cost effective and can yield good diagnostic accuracy in diagnosing meningitis.

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