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Evaluation of Using Urine Reagent Strips in the Diagnosis of Childhood Meningitis

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Abstract

Background: Bacterial meningitis is a serious infection of the central nervous system. Rapid diagnosis and prompt treatment remain the cornerstones of management of patients with meningitis. On the other hand, aseptic meningitis is a benign self-limited disease. Differentiating both diseases is of great importance. The main aim of this study was to evaluate the usefulness of urine reagent strip tests in the diagnosis of meningitis.

Patients and methods: Fifty children aged 1-18 years with mean 6.53+4.55years were included. They clinically suspected to have meningitis from Benha university hospitals and shebin El Koom Fever Hospital in the period from April 2015 to March 2016. CSF samples were tested using both Combur-10 urinary reagent strip and CSF microscopy examination as reference standards. Combur-10 was used to estimate ten parameters including protein, glucose, and leukocytes.

Results: The diagnostic accuracy of protein estimation by reagent strip show 100% sensitivity, 3.7% specificity for detection of CSF proteins at level 100, while the specificity was 50% at level 47. Proteins (greater than 100 mg/dl), Glucose reagent strip positivity had 96.8% sensitivity and 100% specificity for detection of CSF glucose at level 46 mg/dl. Leukocyte esterase positivity by test strip had sensitivity of 100% and specificity of 75% for the detection of CSF granulocytes of more than 10 granulocytes/mm. There was no significant difference as regard age, sex and clinical presentation between septic and aseptic meningitis. There was significant increase in CSF parameters (leucocyte, protein) by both method and high significant increase in glucose in septic than aseptic.

Conclusion: Urinary reagent strips can be used to diagnose meningitis, especially in low-resource settings and urine strips offers a clinically useful and rapid screening method for the quantitative determination of CSF; glucose, protein and leukocytes. The advantages include ease performance and ready availability.

Keywords: Children meningitis, Urinary reagent strip, Cerebrospinal fluid

Introduction

Bacterial meningitis is an existence undermining neurological condition and needs incite parental anti-infection agents, while viral meningitis is a benign condition with a good outcome [1]. Cerebro-spinal fluid (CSF) microscopy, CSF chemistry, and microbiological studies are required to make the diagnosis of meningitis. An experienced microscopist is required to estimate the CSF cell count, while reasonable laboratory support is required to estimate sugar and protein levels. These offices are regularly not accessible in asset-restricted settings, and even in settings where these are available, turnaround times are long. Currently, no rapid point-of-care tests are available to detect meningitis [2]. The use of easily applicable tests that can determine whether antibiotic therapy will be necessary must be stimulated. The aim of this study was to evaluate the use of an extremely easy method, in which results can be obtained through a reaction within seconds. The use of reagent test strips as a routine procedure may be considered as a useful complementary method for the prompt diagnosis of bacterial meningitis in cases where sufficient CSF is not easily obtained or in cases where quick decision for antibiotic therapy must be taken immediately [3].

Patients and Methods

Patients

This study was conducted on 50 children 1-18years old with mean age 6.53+4.55. They were clinically suspected to have meningitis from pediatrics department, Benha university hospitals and shebin El Koom Fever Hospitals in the period from April 2015 to March 2016. Diagnosis of meningitis was based on the clinical picture, examination and confirmed by CSF analysis. The study was approved by the Ethical Research Committee, Faculty of medicine, Benha University.

Methods

We obtained 3 ml of CSF and the sample was divided into three parts; first part for strip, second for laboratory as a reference standard and last for culture. Reagent strip analysis was carried out immediately. Combur-10 (Roche Diagnostics, Basel, Switzerland) was a 10-patch strip used to test CSF. This strip was used to detect CSF cellularity (leukocyte esterase estimation), glucose (glucose oxidase-peroxidase method), and protein levels (protein error of indicator). All tests were performed blindly to compare with the results of the reference standard.

Utilized one to two drops of CSF, attracted a pipette, and poured these on glucose, protein, and leukocyte patches to note the color changes.

Urine reagent strip test

A. Cerebrospinal fluid leukocytes: A normal CSF WBC count is <5 cells/mm^3, and the reagent strip needs at least 10 cells for recognition and has an upper detection limit of 500 cells/mm^3. Undiluted CSF was used and the test result was interpreted using the manufacturer-provided color grading (less than 10 granulocytes/mm^3: no shading, 10-75 granulocytes/mm^3: 1+, 75-500 granulocytes/mm^3: 2+, >500 granulocytes/mm^3: 3+).

B. CSF glucose: A typical CSF glucose level is 66% of the plasma glucose. The levels of CSF glucose fall in bacterial and contagious meningitis. The interpretation of results on a reagent strip was no change in color if less than 50 mg/dl (yellow) and any change in color if more than 50 mg/dl (green).

C. CSF protein: Normal CSF proteins range between 15 and 45 mg/dl and the range for protein detection of the strip is between less than 30 mg/dl to 500 mg/dl. The understanding of most extreme shading on reagent strip was: under 30 mg/dl: no adjustment in shading - around 30 and 100 mg/dl: 1+ -between 100 and 500 mg/dl: 2+ - and more than 500 mg/dl: 3+ **(Table 1)**.

Reference test

Total CSF cell counts were performed by microscopy (using a Neuberger's chamber), within 1 h of collection of CSF sample. Differential cell counts were performed on Giemsa-stained, cytocentrifuged CSF sample. CSF sugar and protein levels were analyzed by conventional biochemistry.

Results

This study included 50 children, their age were (1-18) years old with mean age 6.53+4.55, male was 56% and females were 44% **(Table 2)**.

Table 1 Urine reagent strip test

Strip test	Reference standard (laboratory)
-Leucocyte reagent strip	**-CSF microscopic**
No color	Less than 10 granulocytes/mms
Any color	10 or more 10 granulocytes/mms
More color on color scale	75 or more 75 granulocytes/mms
-Glucose reagent strip	**-CSF Biochemistry Glucose**
No color	Less than 50 mg/dl
Any color	More than 50 mg/dl
-Protein reagent strip	**-CSF Biochemistry protein**
No color	Less than 30 mg/dl
Any color	More 30-100 mg/dl
More color on color scale	More than 100 mg/dl

Table 2 Demographic criteria of study groups

	No (50)	%
Age mean ± SD (Range)	6.53 ± 4.55 (1-18)	
Male	28	56.0
Female	22	44.0

Leukocyte esterase positivity by test strip had sensitivity of 100% and specificity of 75% for the detection of CSF granulocytes at cut off 10 cells/µl.

Protein reagent strip shows 100% sensitivity, 3.7% for the detection of CSF proteins at cut off 100 mg/dl, while the specificity was 50% at cut off 47 mg/dl. Specificity decreased when we used a higher cut off detection of 2+ or higher of CSF proteins (greater than 100 mg/dl).

Glucose reagent strip positivity had 96.8% sensitivity and 100% specificity for detection of CSF glucose at cutoff 46 mg/dl **(Table 3)**.

Table 3 Diagnostic accuracy of reagent strip for detection CSF leucocyte, glucose and protein

	Positive	Negative	Sensitivity	Specificity	PPV	NPV	Accuracy	FET	P value
CSF Leucocytes									
>10 cells/ul	46(100%)	0(0%)	100%	75%	97.9	10			
≤10cells/ul	1(25%)	3(75%)				0.0	98.0	24.61	0.001**
CSF Protein									

≤100.0 mg/dl	26(96.3%)	1 (3.7%)	100%	3.7%	46.9	10	48	0	1
>100.0 mg/dl	23 (100%)	0(0%)							
CSF Protein									
≤47.0 mg/dl	1 (50%)	1(50%)	100%	50%	98	10	98	5.62	
>47.0 mg/dl	48(100%)	0(100%)				0			0.018*
CSF glucose									
<46 mg/dl	0(0%)	19(100%)	96.8%	100%	100	95	98	42.02	0.001**
≥46 mg/dl	30(96.5%)	1(3.2%)							
FET: Fisher Exact Test; CSF: Cerebrospinal fluid.									

Patients were classified into group I bacterial (septic) and group II aseptic according to the following criteria [2] **(Table 4)**.

Table 4 Bacterial and viral classification

Type of meningitis	Definition of meningitis	Findings
Bacterial (septic)	Gram stain and/or antigen detection and/or CSF cultures Or positive blood culture with meningitis CSF polymorphnuclearcytosis	Glucose <50 mg/dl; protein >500 g/l; and any number of cells or glucose >50 mL; protein >500 g/L and cell count >=500 cell/ml
Viral (aseptic)	Clinical and laboratory features of aseptic meningitis negative cultures	Glucose 50-100 ml; any amount of protein, and cell count of 10-75 cells/ml

There were a highly degree of agreement (positive correlation) between strip and laboratory in leukocyte count, protein and glucose in studied groups in different strip degree and significant difference between both groups septic and aseptic group was found for CSF leukocyte, protein and glucose **(Table 5).**

Statistical analysis

Data were collected and statistically analyzed using SPSS version 16 statistical package. Comparison of qualitative data was performed with chi square (x^2) test. The validity of screening tests were measured and expressed as sensitivity, specificity, accuracy, positive predictive value, and negative predictive value (in comparison to diagnostic tests). The level of significance was considered at 5%. The highly significant level was at <0.01 or less.

Table 5 This table shows comparison between septic and aseptic groups as regards CSF analysis results (laboratory and strip)

CSF Leucocytes Strip leucocytes	Mean ± SD	Range	F-test	P-value
Septic group				
-(3)	7.33 ± 1.53	6-9	69.49	0.001**
+(16)	30.11 ± 19.29	10-61		
++(9)	248.33 ± 131.14	79-450		
+++(11)	805.27 ± 239.0	500-1375		
Aseptic group				
+(7)	52.14 ± 17.98	15-70	949.0	0.001**
++(3)	86.33 ± 10.6	75-96		
+++(1)	812.0 ±-	812-812		

CSF Protein	Mean ± SD	Range	F test	P value
Strip protein				
Septic group				
-(1)	23.7	23.7-23.7	58.48	0.001**
+(20)	71.28 ± 14.46	40-97.5		
++(15)	232.15 ± 111.5	101-427		
+++(3)	632.0 ± 46.23	600-685		
Aseptic group				
+(6)	78.83 ± 14.76	57-95	77.22	0.001**
++(4)	242.0 ± 87.87	153-333		
+++(1)	811.0 ±-	811-811		
CSF Glucose	**Mean ± SD**	**Range**	**F test**	**P value**
Strip glucose				
Septic group				
-(20)	32.2 ± 9.09	18-48	67.31	0.001**
+(19)	64.11 ± 14.68	50-110		
Aseptic group				
+(8)	79.5 ± 17.31	55-98	4.72	0.058
++(3)	103.67 ± 12.9	93-118		

Discussion

Acute bacterial meningitis is one of the most severe and potentially life-threatening infectious diseases. No rapid diagnostic tests exist for the analysis of CSF [4].

This study was conducted on 50 children clinically suspected to have meningitis. Those patients were 28 males (56%) and 22 females (44%) They were classified as follows; 39 case with septic meningitis group (I) and 11 with aseptic meningitis group (II). Concerning symptom in the present study fever was the most frequent symptom 92%. These results agree with Ibrahim et al. [5] who found that 95% of the patient with bacterial meningitis presented by fever and Choi et al. [6] who found that 92.9% of the patients of aseptic meningitis also had fever.

The present study demonstrated that vomiting was present in 38.5% in the group (I). This finding was lower than Abdul rab et al. [7] who found that among the patients with bacterial meningitis 53.7% had vomiting. And 36.4% in the group (II) had vomiting less than Choi et al. [6] who found that among cases of aseptic meningitis 54.8% had vomiting.

In our study headache was present in 59% in (Group1) this finding agrees with Abdul rab et al. [7] who found that among the patient with bacterial meningitis 56.1% had headache.

Altered level of consciousness was present in 89% of septic meningitis (group I) cases and 72% of aseptic cases (group II), this agrees with Hsu et al. [8] whose study on 40 patients, they found that deterioration in consciousness was the most common clinical presentation (100%) in patients of septic meningitis and this difference may be explained by extensive utilization of antibiotics before admission delay diagnosis in 61.7% of septic meningitis patients in our study.

In our study convulsion was noted in 23% of cases with septic meningitis and in 9.1% of aseptic meningitis. Aseptic group finding disagrees with Hatamian and Fahimzad [9] who study viral meningitis and found convulsion in 19% of their cases, on the other hand Michos et al. [10] found in their study on 506 child with aseptic meningitis that seizures present in 2.3% only.

Our study showed that signs of meningeal irritation including neck rigidity, positive Kerning's and Brudzenisky sign were present in 92%, 33% and 33% of cases of acute septic meningitis and in 90.9%, 45.5% and 45.5% of aseptic cases respectively. These results were agree those reported by Ndreu et al. [11] who found that neck rigidity, positive Kerning's and Brudzenisky sign were present in73.1%, 55.2% and 56.7% of cases of acute septic meningitis respectively. But our results disagree with Michael [12] who found that neck rigidity in cases of aseptic meningitis is higher than cases with septic meningitis. The mean value of CSF leucocytic count in Group I (septic group) was (417.63 cell/dl) with granulocytes predominance (68.51%), and in Group II (aseptic group) CSF leucocytic count was (130.55 cell/dl) with lymphocyte predominance (70.36%) with highly significant difference between both groups.

Regard microbiological examination in our study only 16 case (32%) in Group (1) were gram +ve and 23 (46%) were gram variable coccobacilli, disagree with Makoo et al. [13] who found organism in very few cases (16%). In our study, 39 patients were diagnosed with bacterial meningitis and the most frequent bacteria isolated were *Haemophilis influenza* (46%), streptococci (4%) and pneumococci (28%).

Disagree with the study of Joshi et al. which reported a frequency of 11% for Streptococcus in CSF sample of meningitis 11 patient's. This reason for this difference may be due to their vaccination program.

Our study show high degree of agreement between reference and urine reagent strip regarding leucocytic count, protein and glucose in all studied groups and in different level, agree with this result of Parmer et al. [14].

The results of our study found that, Combur-10 strips can determine CSF neutrophil count more than 10/mm^3, CSF protein levels more than 47 mg/dl and more 100 mg/dl, and CSF glucose levels less than 50 mg/dl with reasonable accuracy.

Leukocyte esterase positivity by test strip had a sensitivity 100% and specificity 75% for detection of CSF granulocytes at level 10 cells /mm. Reagent strip showed sensitivity 100%, specificity 3.7% for the detection of CSF proteins at level 100(++), while the specificity was 50% at level 47(+). Specificity decreased when we used a higher level detection of 2+ or higher CSF proteins (greater than 100 mg/dL). Glucose reagent strip positivity had sensitivity 96.8% and specificity 100% for the detection of CSF glucose at level 46 mg/dL.

Observations of our study were comparable to those reported by Joshi et al. [2] using the same reagent strip, they observed sensitivity 85.2% and specificity of 89.6% for leucocytes >10 cells/mm. For proteins, at a cut-off of ≥30 mg/dl, the sensitivity was high (98.1%) but the specificity was low (57.1%); however, at a cut of ≥100 mg/dl, both the sensitivity and specificity were high and acceptable (as observed in our study except in protein).

The strip-based analysis for glucose at a cut-off of ≤40 mg/dl was more specific (96.5%) than sensitive (61.1%); and, even at a cut-off level of ≤50 mg/dl, the test was more specific (98%) than sensitive (46.2%). That may be due to all cases had CSF glucose less than 50(-ve) [15] in their study, observed a positive correlation between the strip and laboratory values for the diagnosis of meningitis with for cells, protein and glucose, which was statistically significant. Parmar et al. [14] in their study on 63 CSF samples observed a high sensitivity for the diagnosis of bacterial and tubercular meningitis, (100% and 96.55%), respectively and for the diagnosis of aseptic meningitis, the strip was more specific than sensitive. Romanelli et al. [3] observed the sensitivity of 90.7%, specificity of 98.1%, for the results of the reagent strip analysis in the diagnosis of bacterial meningitis, was statistically significant with P value<0.0001 [16]. An issue in utilizing these strips is the distinctive shorts for protein and glucose values for CSF and urine analysis. These strips can be designed to indicate clinically meaningful cutoffs for CSF analysis. The cutoffs for urine analysis are 30, 100, and 500 mg/dl. These can be modified to 30, more 100, and 500 mg/dl, as a CSF protein level of more than 45 mg/dl is considered abnormal. Similarly, since a low CSF glucose is clinically more meaningful, the lowest cutoff for CSF sugar detection can be made to be 47 mg/dl rather than 50 mg/dl in the current strip.

The strips may be designed to include only three parameters for proteins, glucose, and granulocytes, as opposed to the 10 for urinary investigation, in this manner chopping down the expense of these tests and making the CSF strip analysis more cost effective.

The general similar and specificity of strips in our study was around 97.14% and 96.42% individually [3]. The affectability and specificity were low just in instances of aseptic meningitis, where affectability is somewhat low up to 70% however; specificity is great being 96.55%. To judge the benefits of various reagent strips for reproducibility in CSF.

Parmar et al. [14] conducted a study with 68 patients, in which they separately analyzed sensitivity and specificity for each of the items analyzed by the reagent strips, thus validating the test for the diagnosis of bacterial meningitis. These authors pointed out the necessity for the presence of polymorph nuclear leukocytes, which have esterase, an enzyme that reacts with the color [17]. As regards the urine reagent strips, they found that the number of reagent strips results coinciding with the laboratory results (values that fell within the range set by the cut-off points previously determined), that was, the concordance rate between the laboratory assay and reagent strips results was 72% for leukocytes, 64% for protein, and 49% for glucose.

The study of Koulaouzidis [18] became caution was needed in the use of reagent strips for the diagnosis of meningitis, because this test is subjective, especially in cases with slightly altered CSF; therefore, the method is considered qualitative or semi-quantitative.

Our outcomes demonstrate that the quick diagnosis of meningitis can be made with the Combur-10 reagent strips with a high specificity and sensitivity.as test can help in the making the rapid decision whether to use or withhold antibiotics in patients with meningitis. It is easy to do and would be of particular value in developing countries where no laboratory facilities exist also, Urine reagent strips may help as a complementary method for guiding the physicians in deciding a management until the standards results are available.

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