

# Comparison of CSF Serum Albumin Index with CSF Glucose and CSF proteins in Bacterial and Viral Meningitis

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## ABSTRACT

**Background:** Meningitis is one of the severe inflammation of coverings of Brain and Spinal cord in developed countries with serious sequelae. With routine diagnostic procedures delay in diagnosis of meningitis may cause with grave result for the patients. To speed the diagnostic procedures a new diagnostic measure the cerebro spinal fluid serum albumin index has been introduced in detection of meningitis.

**Aim:** To compare Cerebro Spinal Fluid Serum Albumin Index with CSF Glucose and CSF proteins in determination of bacterial and viral meningitis.

**Methods:** A comparative cross section study was conducted in department of PNS Shifa Karachi from March 2014 to August 2015 on 190 patients of 1-16 years of both sex with history of sign and symptoms of disease i.e., fever, headache, neck rigidity which were included in the study.

**Results:** The summarized results of study showed the mean age as 13.875±1.414 years. Mean of CSF albumin is .4299 g/l with SD 0.44353 while serum albumin in g/l mean is 38.03 and SD 4.488 and mean of CSF-serum albumin index is 11.7321. In student T test for CSF serum albumin index the mean of CSAI was 7.47±0.5. The sensitivity of the test is 91.09% and specificity is 96.4% while diagnostic accuracy is 94%.

**Conclusion:** It is concluded that CSAI is a cost effective and efficient laboratory test for early diagnosis of bacterial and viral meningitis.

**Keywords:** Cerebro Spinal Fluid (CSF), Cerebro Spinal Fluid protein, CSF Serum Albumin.

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## INTRODUCTION

Blood brain barrier (BBB) is formed at three sites between blood and central nervous system<sup>1</sup>. It includes BBB, blood Cerebro Spinal Fluid (CSF) barrier and arachnoid barrier. The cells constituting BBB are endothelial lining cells of arterioles, capillaries, veins and epithelial surfaces of choroid plexus and it is the major site of blood CSF exchange<sup>2</sup>. Pericytes with astrocyte plays an important role in<sup>3,4</sup> the regulation of BBB. The most important function of BBB is isolating and protecting nervous tissue of the brain and spinal cord from fluctuation in nutrients, hormones, metabolites and other blood constituents<sup>5</sup>. The blood brain barrier (BBB) and the sophisticated tight junctions restrict the bacterial entry to the CNS. The most common cause of disruption of BBB is meningitis<sup>6</sup>.

The incidence of meningitis in Pakistan is 14632 out of 159,196,336 population<sup>7</sup>. The etiology of meningitis include both infectious and noninfectious causes<sup>1</sup>. Infectious variety is caused by bacteria, viruses and fungi and this upon complication may

result in septic meningitis. Noninfectious variety results in aseptic meningitis, the events involved in the development of disease include bacterial invasion<sup>8</sup>, inflammatory response<sup>9</sup> and neuronal damage<sup>10</sup>. The majority of the symptoms produced because of bacterial meningitis, are as a result of inflammatory response to invading organisms<sup>11</sup>. Bacterial meningitis may result in severe complications with brain damage, hearing loss and hearing difficulties<sup>12</sup>.

Previously increased concentration of protein and decreased concentration of glucose in CSF is considered diagnostic for bacterial meningitis<sup>13</sup>. Recent studies showed that evaluation of albumin in CSF and serum specimen obtained at the same time can predict disruption of BBB and meningitis<sup>14</sup>. Increased amount of specific plasma protein in CSF is neither synthesized, nor metabolized intrathecally so in CSF which is free of contaminating blood so albumin in CSF must come from plasma through BBB<sup>15</sup>. The reason of conducting this study is that no previous study has been carried out for the importance of CSAI in Pakistan. The purpose of this study is to establish the utility of CSAI in disruption of BBB and in meningitis. So this study will facilitate earlier diagnosis of meningitis which can lead to prompt treatment and less complications.

Aim of this study is to compare Cerebro Spinal Fluid Serum Albumin Index (CSAI) with CSF Glucose

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and CSF proteins in determination of in bacterial and viral meningitis

## MATERIALS & METHODS

This cross sectional study was done at the department of chemical pathology at PNS Shifa hospital Karachi. The duration of this study was from March 2014 to March 2015. 190 Patients of any gender were included in the study with age range of 1-16 years. Meningitis was diagnosed on clinical findings such as fever, headache or neck rigidity and lab findings such as CSF gram staining, CSF culture and chemical analysis. Bacterial meningitis was defined when CSF was cloudy, by a positive result on gram staining and/or bacterial culture and polymorph leukocytosis with leukocyte count in CSF was  $>1500/\text{mm}^3$  with granulocytes representing  $>50\%$ . Meningitis was defined viral when meningitis sign and symptoms were present with negative blood culture and negative gram staining with CSF pleocytosis i.e., 20-1000 WBC comprised mainly of lymphocytes. Patient with clinical diagnosis of meningitis and CSF Gram's staining and/or CSF culture positive for bacteria or patient with clinical and CSF findings suggestive of meningitis with negative CSF Gram's staining and culture were included in the study<sup>16</sup>. Exclusion criteria included all the patients who received antibiotics before presenting to the hospital or patients with Tuberculosis and fungal meningitis. All the patients were treated according to the current guidelines of bacterial and viral meningitis. 2.5 ml of venous blood sample from each patient in plain sample tube was taken from the patient. Serum was obtained to determine the serum albumin level on Roche Modular P800, by automated dye binding method of Bromocresol green (BCG) dye, using Roche reagent kit calibrator and controls. The CSF sample obtained from each patient by lumbar puncture. CSF was analyzed for albumin, protein and glucose respectively. CSF Albumin is measured by micro albumin method via immunoturbidimetry on Roche Modular P800 while CSF protein is measured by Biuret Method. The CSF Glucose was analyzed by Glucose Oxidase Per Oxidase method on modular p800. Using the results of quantitative albumin assays the following ratio was calculated by following formula. A p value of  $<0.05$  was taken as significant in all statistical analysis.

$$\text{CSF/Serum Albumin index} = \frac{\text{Albumin CSF (g/dl)}}{\text{Albumin serum (g/dl)}} \times 1000$$

## RESULTS

A total of 190 patients which fulfilled the inclusion criteria were included in the study. The mean age  $\pm$  SD of the patients under this study was 5.9 years  $\pm$  3.4 years. Males were more i.e., 108(56.8%) while females were 82(43.2%). Fever, headache and

altered sensorium were the most common presenting symptoms. While signs of meningeal irritation i.e., positive brudzki or burnings signs were present in most of the patients. Out of the 190 patients, 49 cases (25.7%) were suspected of bacterial or viral meningitis but were diagnosed later on as Encephalitis, Non infectious meningitis or Hydrocephalus etc. 93(48.9%) had bacterial meningitis whereas 48(25.2%) had viral meningitis. Among the 93 bacterial meningitis patients, Strept. Pneumoniae was isolated in 36(38.7%), Meningococci was isolated in 18(19.35%), Staph. Aureus in three (3.22%), Klebsiella Pneumoniae in two (2.15%), E.Coli in 1(1.07%) and Strept. Agalactiae in 1(1.07%) patient. In twenty three (25.58%) patients no organism was isolated (culture - ve bacterial meningitis) but CSF changes were suggestive of bacterial meningitis and these patients were treated with antibiotic. The CSF protein level was high in bacterial than viral meningitis patients, with mean  $641.01 \pm 428.52$  vs.  $91.74 \pm 44.68$  mg/dl (p value  $<.0001$ ). The CSF leukocyte count was higher with predominant polymorphs (95%) in bacterial than viral (7%) cases, with mean cell count  $4522.25 \pm 2809$  vs.  $206.31 \pm 218.93$  cell/mm<sup>3</sup> (p value  $<.0001$ ). In comparison to the viral, the CSF glucose level was found to be lower in bacterial meningitis, mean  $26.50 \pm 21.56$  vs  $67.00 \pm 18.96$  mg/dl, with statistically significant difference (p value  $<.0001$ ). In the bacterial group, 50% of the patients had CSF glucose  $<10$  mg/dl, whereas none of the patient with viral meningitis had such low CSF glucose level. The blood glucose and peripheral leukocyte count was also high in bacterial than viral meningitis,  $179.49 \pm 55.10$  vs  $135.21 \pm 39.31$  mg/dl and  $20.76 \pm 8.02$  vs  $8.90 \pm 2.25$  cell/cul respectively (p value  $<.0001$ ). The leucocytosis was present in 91% of the patients in bacterial; whereas only 17% of the viral meningitis cases had mild elevation of white cell count. Mean of CSF albumin in g/l is 0.4299 while serum albumin in g/l mean is 38.03 and SD 4.488 and mean of CSF-serum albumin index is 11.7321. Mean of serum albumin mean was  $39 \pm 0.2$  mg/dl and SD 4.488. In student T test for CSF-serum albumin index the mean of CSAI was  $7.47 \pm 0.5$ .

## DISCUSSION

Meningitis is inflammation of coverings of spinal cord and brain, which is caused by microorganism including bacteria fungi, viruses and mycobacterium tuberculosis. The symptoms and signs of meningitis are often non specific. CSF findings are important in the differential diagnosis of patients with bacterial and viral meningitis<sup>9</sup>. Due to meningitis the result is disruption of BBB which was previously measured by CSF culture, CSF Protein concentration or CSF glucose concentration and CSF cell count. CSF

culture is a costly and time consuming procedure. Gram's stains of spinal fluid are virtually diagnostic of bacterial meningitis when microorganisms are seen, but negative results of initial Gram's staining do not exclude the diagnosis. The Gram stain is positive in 60% to 90% cases of untreated bacterial meningitis. All lab does not have capability to perform CSF culture. Any delay in diagnosis of meningitis can be fatal for the patient while CSF glucose or CSF protein are not reliable. So we compare CSF glucose and CSF protein concentration with newer lab tests such as CSAI<sup>17</sup>. CSAI is a cost effective lab diagnostic tool can be performed easily by measuring CSF albumin with serum albumin. CSAI can lead to early and timely diagnosis and help to differentiate bacterial from viral meningitis<sup>18</sup>.

Results of the study showed that 95% of the patients with bacterial meningitis had predominant polymorphs, where as only 7% of the patients with viral meningitis had polymorphs pleocytosis. The hospital stay was longer in bacterial than viral meningitis,  $9.25 \pm 3.40$  vs  $6.82 \pm 2.73$  days ( $p$  value  $< 0.0001$ ). The findings of the studied case series is consistent with the above observation and  $> 50\%$  of the patients with bacterial meningitis had CSF glucose  $< 10$ mg/dl, where as none of the patients with viral meningitis had such low CSF glucose level. Different studies showed that significant increase in CSF protein level in bacterial meningitis as compared to the viral meningitis. In bacterial meningitis white cell count, usually polymorphs, increases significantly, where as there is mild increase in cell count, mostly lymphocytes in viral meningitis.

The summarized results of study showed the mean age as  $13.875 \pm 1.414$  years and mean of CSF albumin in g/l is .4299 with SD .44353 while serum albumin in g/l mean is 38.03 and SD 4.488 and mean of CSF-serum albumin index is 11.7321. In student T test for CSF-serum albumin index the mean of CSAI was  $7.47 \pm 0.5$  with SD 14.4004. The sensitivity of the test is 91.09% and specificity is 96.4% while diagnostic accuracy is 94%, which is a characteristic of a good test. The results of CSAI are in accordance with international studies as studied by Blyth BJ<sup>25</sup> which showed that CSF/Serum Albumin Index value of  $< 9$  is considered consistent with an intact blood brain barrier, values 9 to 14 are interpreted as slight impairment and 14 to 30 as moderate impairment and  $> 30$  as severe impairment of BBB<sup>19</sup>.

## CONCLUSION

CSF analysis is an important diagnostic test to differentiate bacterial from viral meningitis. The

diagnostic capabilities of conventional CSF variables (proteins, glucose and cells) is limited. The CSAI can provide a cost effective and reliable laboratory test which is very useful in distinguishing bacterial from viral meningitis. CSAI is rapid diagnostic test with higher sensitivity and positive predictive value.

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