Cerebrospinal Fluid C-Reactive Protein and Adenosine Deaminase Levels in the Differential Diagnosis of Meningitis in Adults

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ABSTRACT

Introduction: Acute infections of the Central Nervous System like Meningitis and Encephalitis, need to be diagnosed promptly because early institution of treatment would not only be life saving but also reduce consequent neurological impairment. This study was aimed to assess the signicance of estimation of Cerebrospinal Fluid C-Reactive Protein and Adenosine Deaminase levels in differential diagnosis of meningitis in adults.

Material and Methods: This study was carried out in the department of Medicine at Shri Sayaji General hospital, where we enrolled 50 patients presenting with symptoms and signs of meningits. Routine and microscopic examination of of CSF was done, alongwith CSF ADA and CRP.

Results: Out of total 50 patients, 23 had tubercular meningitis, 6 had pyogenic and 21 had viral meningitis.The mean ADA activity in the tubercular group was significantly higher than in other groups. The CRP levels were significantly higher in pyogenic meningitis as compared to the other two groups.

Conclusion: High CSF ADA and CSF CRP can be used to differentiate between tubercular, pyogenic and viral meningitis. High ADA levels are suggestive of tubercular meningitis High CSF CRP levels are suggestive of Pyogenic meningitis, both of which are reduced in viral meningitis.

Keywords: Tubercular, Pyogenic, Viral

INTRODUCTION

Meningitis is infection within the sub arachnoid space. The common causes of meningitis could be bacterial, viral or tubercular.The classic clinical triad of meningitis is fever, headcahe and nuchal rigidity, however the triad may always not be present.[1] Acute Meningitis leads to significant mortality and morbidity. Bacterial meningitis can lead to decreased intellectual function, memory impairment, seizures, hearing loss and gait disturbances.[1] Common neurological complications seen with tubercular meningitis are hydrocephalus, stroke, cranial nerve palsies, epileptic seizures.[2]

Cerebrospinal fluid analysis with special regard to ADA is specifically used to diagnose tubercular meningitis, in which it is raised. ADA is released by T-cells during cell mediated immune response to the tubercle bacilli.[3] ADA levels in CSF is useful in differntiating tubercular from non tubercular meningitis,[4,5] CSF C reactive protein levels are elevated in patients of pyogenic meningitis.[6,7] In this study we used these two parameters of CSF analysis to differentiate amongst viral, bacterial and tubercular meningitis.

MATERIAL AND METHODS

This was a prospective cross sectional study carried out in the Department of Medicine at the Shri Sayaji General Hospital and Medical college, Baroda. We enrolled 50 patients having clinical features suggestive of meningitis.Patients or their relatives were explained regarding the study and after taking the written informed consent, detailed history was taken and examination was done. A battery of routine investigations were done and CSF was drawn and sent for routine and microscopic examination,alongwith CSF ADA and C-reative Protein.Based on clinical, laboratory and CSF analysis, patients were divided into Pyogenic, Tubercular and Viral meningitis.

Clinical diagnosis of Meningitis was made in those having triad of fever, headache and nuchal rigidity, alongwith Nausea, vomiting, photophobia, with or without altered mental status or seizures; who on examination had positive Kernig's and Brudziniski's sign. Those patients having clinical features of meningitis and age more than 18 years were included in the study,while those having fungal meningitis, in whom lumbar puncture was contraindicated,patients on steroids, severe hepatic dysfunction and age less than 18 were excluded from the study. On the basis of clinical and laboratory reports, patients were divided into three groups.

Criteria for diagnosing different types of meningits

Pyogenic meningitis: usually acute in onset, may be associated with sinusitis, otitis media. Csf analysis having Proteins>45mg/dl, Sugar <40mg/dl or less than 40% of the blood glucose concentration, pleocytosis>250cells/cmm predominantly neutrophils. Neuroimaging may show diffuse meningeal enhancement, abscesses or parameningeal focus.

Tubercular meningitis: usually insidious in onset, may be associated with tuberculosis of other organs. CSF analysis showing Proteins>45mg/dl, Sugar<40mg/dl or less than

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40% of blood glucose concentration,pleocytosis > 10 cells/cmm predominantly lymphocytes. Neuroimaging may show meningeal enhancement, basal exudates and /or tuberculoma. Viral meningitis: usually acute in onset. CSF analysis showing Proteins>45mg/dl, Sugar normal range, lymphocytic pleocytosis>25 cells/cmm. Neuroimaging may reveal diffuse meningeal enhancement.

STATISTICAL ANALYSIS

Descriptive statistical analysis was carried out; results on continuous measurements were presented on mean+_SD and results on the categorical measurements were in the numbers(%). Sensitivity, specificity, NPV and PPV were calculated for CSF CRP and ADA levels to know the association with type of meningitis. P value of < 0.001 was considered significant.

RESULTS

We had enrolled 50 patients of meningitis, who were then grouped into three depending on the type of meningitis, based on the clinical features and CSF analysis. We had 23 patients (46%)of tubercular meningitis, 21 patients(42%) of Viral meningitis and 6 patients (12%)of Pyogenic Meningitis.

On analysing the CSF ADA levels, it was observed that the ADA levels were significantly elevated in patients with Tubercular meningitis, the mean value being 14.37+_6.38IU/l. The mean ADA levels in patients with pyogenic and viral meningitis were 4.02+_1.98IU/l and 1.65+_1.66IU/l, respectively. The Sensitivity and specificity of ADA levels, in relation to Tubercular meningitis was 82.61% and 100%, respectively, with a NPV of 87.10%, PPV of 100% and Accuracy of 92%. This value was statistically significant with a p value of <0.001.

On analyses of CSF C-reactive protein levels, it was noted that they were significantly elevated in patients with Pyogenic meningitis, the mean value of which was 31.33+_6.06mg/dl.The patients with tubercular and viral meningitis had mean CRP level of 1.30+_0.52mg/dl and 1.21+_0.3mg/dl respectively.The Sensitivity and specificity of CSF CRP levels in relation to pyogenic meningitis was 83.33% and 93.18% respectively, with a NPV of 97.62%, PPV of 62.50, with an accuracy of 92%. This value was statistically significant with a p value of <0.001.

DISCUSSION

The clinical diagnosis of meningitis can be made promptly, but to differentiate amongst the various types of meningitis, on the basis of routine CSF analysis, at times may be a challenging task.Early diagnosis is important considering the mortality and complications associated with delay in onset of treatment.

To diagnose Tubercular meningitis, definatively,it is required to demonstrate presence of Acid Fast Bacilli on smear or culture. Culture of AFB takes 4-6 weeks and AFB staining is not sensitive enough. Rapid diagnostic test with good sensitivity and specificity are required for early and definative diagnosis of Tubercular meningitis.[8] Increased level of ADA in the CSF has been found to be useful in diagnosing Tubercular meningitis. ADA catalyzes the deamination of adenosine and deoxyadenosine to inosine and deoxyinosine, respectively.There are two isoenzymes, ADA1 and ADA2. ADA1 is found in all cells with highest activity in lymphocytes and monocytes, while ADA2 is found only in monocytes.[9] ADA has been considered a marker of cell mediated immunity and its activity has been observed in various infections including Tubercular meningitis. As both humoral and cell mediated immunity play a role in Tubercular meningitis, ADA activity in CSF has been found to be useful in differentiating tubercular from non tubercular meningits.[3]

In our study we found significantly increased levels of ADA in CSF in the patients of tubercular meningitis, the mean ADA being 14.37+_6.38.The mean ADA levels were 4.02+_1.98 in pyogenic meningitis and 1.65+_1.66 in viral meningits, suggesting that increased ADA levels support the diagnosis of Tubercular meningitis and low levels suggest non tubercular aetiology.

Sang-Ho Choi et al[10] studied ADA activity in CSF of 182 patients with meningitis and found the mean ADA levels in tubercular group to be 12.7+_7.5, which was significantly higher than in other groups (3.10+_2.9IU/l; p<0.001). In a study by Belagavi et al(11), the mean ADA levels in tubercular group was 14.14+_7.44IU/l as against lower levels in pyogenic(3.80+_1.92IU/l) and viral meningitis(1.85+_1.43IU/l).

Several other are in agreement with our observations, such as a study by Kashyap et al[12] who studied 117 patients of meningitis and found an increased ADA activity in CSF, the mean being 14.31+_3.87IU/l, in tubercular meningitis pateints.Study by Chotmongkol V et al[13], where they kept the CSF ADA levels cutoff of 15.5IU/l to differentiate tuberculous from non tuberculous meningitis, observed a sensitivity of 75% and specificity of 93%. All the above mentioned studies point to the fact that CSF ADA levels are significantly increased in tubercular meningitis.

C-reactive protein was discovered in 1930 and named so because it caused precipitation of the somatic C-polysaccharide of Streptococcus pneumoniae.[14] It was the first acute phase protein to be described and is an exquisitely sensitive systemic marker of inflammation and tissue damage.[14,15] CSF C-reactive protein levels have been used in quite a few studies to differentiate between pyogenic and non pyogenic meningitis. To diagnose pyogenic meningitis definatively, Gram stain and culture of the CSF for isolating bacteria should be done, which is time consuming. Elevation of C-reactive protein in CSF helps in diagnosing pyogenic meningits.

In our study, we observed that the CSF C-reactive protein levels were significantly elevated in patients with Pyogenic meningitis, the mean value being 31.33+_6.06mg/dl, with a sensitivity and specificity in relation to pyogenic meningitis being 83.33% and 93.18% respectively. The CSF C-reactive protein levels were significantly reduced in patients having tubercular and viral meningitis.

A meta analysis by Gerdes LU et al[16] suggested that a negative

CRP test in either CSF or serum can be used with a very high probability to rule out bacterial meningitis. These findings are supported by another study done by Belagavi et al[11] where the mean CRP in CSF was 33+_5.0mg/dl, 1.09+_0.3 mg/dl and 1.12+_0.48mg/dl in pyogenic, tubercular and viral meningitis patients respectively. A number of other studies by Vaishnavi C et al[17] and Hemavani V et al[18] demonstrate similar findings.Tankhiwale et al[6] studied 75 patients of clinically, biochemically and microscopically diagnosed cases of pyogenic meningitis; 31 had increased CSF CRP levels, of which 27 were culture positive pyogenic meningitis.

Thus, it was found in our study that in tubercular meningitis, the CSF ADA levels were increased but CSF CRP levels were reduced.In pyogenic meningitis, the CSF CRP levels were increased but CSF ADA levels were reduced and in Viral meningitis, both CSF ADA and CRP were reduced.

CONCLUSION

In our study, we enrolled 50 patients of meningitis, who were grouped into Tubercular, Pyogenic and viral meningitis depending on the clinical presentation and routine CSF analysis. On estimating the CSF ADA levels and CSF CRP levels, we observed that ADA was significantly elevated, but CRP was reduced in tubercular patients. Pyogenic meningitis patients had reduced ADA levels with significantly elevated CRP levels in CSF. Viral meningitis had reduced activity if both ADA and CRP levels in CSF analysis.

REFERENCES

1. Roos Karen and Tyler Kenneth, Harrison's Principles of Internal medicine, 18th edition, The Mc Graw Hill Companies, 2012.
2. Anderson NE et al. Neurological and systemic complications of tuberculous meningitis and its treatment at Auckland City Hospital, New Zealand. J Clin Neurosci, 2010;17:1114-8.
3. Gupta BK, Bharat A, Debapriya B, Baruah H. Adenosine Deaminase levels in CSF of tuberculous meningitis in patients. J Clin Med Res. 2010; 2:220-224.
4. Malan C, Donald PR, Golden M, Taljaard JJ.Adenosine Deaminase levels in cerebrospinal fluid in diagnosis of tuberculous meningitis. J Top Med Hyg.1984;87: 33-40.
5. Kashyap RS, Kainthla RP, Mudaliar AV, Purohit HJ, Taori GM, Daginawala HF.Cerebrospinal fluid adenosine deaminase activity: a complimentary tool in early diagnosis of tuberculous meningitis.Cerebrospinal Fluid Res. 2006;3:5.
6. Tankhiwale SS, Jagtap PM, Khadse RK, Jalgaonkar SV. Bacteriological study of pyogenic meningitis with special reference to C-reactive protein.Indian J Med Microbiol 2001;19:159-60.
7. Barry M. Gray, Donald R.Simmons, Henry Mason, Scott Barnum, John E. Volanakis. Quantitative levels of C-reactive protein in cerebrospinal fluid in patients with bacterial meningitis and other conditions. The Journal of Pediatrics 1986;108: 665-670.
8. Chacko F, Modi M, Lal V, Prabhakar S, Rana SV, Arora SK.Diagnostic efficacy of adenosine deaminase levels in cerebrospinal fluid in patients of tubercular meningitis.A comparison with PCR for Mycobacterium Tuberculosis. Annals of Neurosciences. 2010;17:126-130.
9. Jacobus PJ, Ungerer M et al. Significance of Adenosine Deaminase Activity and its Isoeenzymes in Tuberculous Effusions. CHEST 1994;106: 33-37.
10. Choi SH, Kim YS, Bae IG, Chung JW, Lee MS, Kang JM, Ryu J, Woo JH. The possible role of cerebrospinal fluid adenosine deaminase activity in the diagnosis of tuberculous meningitis in adults. Clin Neurol Neurosurg 2002;104:10-5.
11. Belagavi AC, Shalini M. Cerebrospinal fluid C reactive protein and adenosine deaminase in meningitis in adults.J Assoc Physicians India, 2011, Vol 59.
12. Kashyap RS, Kainthla RP, Mudaliar AV, Purohit GJ,Taori GM, Daginawala HF. Cerebrospinal fluid adenosine deaminase activity: a complimentary tool in the early diagnosis of tuberculous meningitis. Cerebrospinal Fluid research 2006 March 30.
13. Chotmongkol V, Teerajetgul GY, Yodwut C. Cerebrospinal fluid adenosine deaminase activity for the diagnosis of tuberculous meningitis in adults. Southeast Asian J Trop Med Public Health 2006; 37:948-52.
14. Pepys MB, Baltz ML. Acute phase proteins with special reference to C-reactive protein and related proteins (pentaxins) and serum amyloid A protein. Adv. Immunol.1983;34:141-212.
15. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. Journal of Clinical Investigation. 2003; 111:1805-1812.
16. Gerdes LU, Jorgensen PE, Nexo E, Wang P. C-reactive protein and bacterial meningitis:A meta-analysis. Scand J Clin Lab Invest.1998; 58:383-93.
17. Vaishnavi C, Dhand UK, Dhand R, Agnihotri N, Ganguly NK. C-reactive proteins,immunoglobulin profile and mycobacterial antigens in cerebrospinal fluid of patients with pyogenic and non tuberculous meningitis. Journal of Hygiene,epidemiology,microbiology and immunology.1992; 36: 317-25.
18. Hemavani N, Chitnis D, Joshi SP. C-reactive protein in CSF and its role in differential diagnosis of meningitis. Ind J Med Microb.2001; 19:26-9.

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