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Review Article

**ROLE OF BIOCHEMICAL TESTS IN DIAGNOSIS
OF CNS DISORDERS**

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ABSTRACT

Laboratory diagnosis particularly biochemical analysis of CerebroSpinal Fluid (CSF) plays a prominent role in the differential diagnosis of various disorders caused to Central Nervous System (CNS) by varieties of bacterial and viruses. CSF remains the corner stone for the diagnosis of different types of meningitis and encephalitis. Routine biochemical measurement done in CSF specimen include proteins, chloride, Glucose and LDH. Many studies carried out in recent times have now recommends measurement of cardiac and liver enzymes and inflammatory markers like C reactive protein, IL-6, Tumor necrosis factor α and certain special proteins. This articles highlights the recent findings in the laboratory diagnosis using CSF and interlink the association of the markers mentioned above in the differential diagnosis of disorder caused to CNS.

KEYWORDS: Central Nervous System, Meningitis, LDH, AST, CRP, IL-6.

INTRODUCTION

Infection of the central nervous system (CNS) can be viral, bacterial, fungal, or parasitic in origin. Infectious microorganisms most often enter the CNS by direct penetration after trauma or by travelling in the bloodstream. Viruses that infect the CNS brain and spinal cord include herpesviruses, arboviruses, coxsackieviruses, echoviruses, and enteroviruses. Infections by these viruses affect primarily the meninges and result in meningitis. Others affect primarily the brain and result in encephalitis. Meningitis is far more common among children than encephalitis. Viruses affect the CNS directly and infect and destroy cells in the CNS resulting in acute illness. After recovery from an infection in the CNS or elsewhere in the body the

immune response to the infection sometimes causes secondary damage to the cells around the nerves.

This secondary damage (postinfectious encephalomyelitis or acute disseminated encephalomyelitis) results in the child having symptoms several weeks after recovery from the acute illness. Prognosis varies greatly with the type of infection. Many types of viral meningitis and encephalitis are mild, and the child recovers quickly and completely. The examination of the cerebrospinal fluid (CSF) has become an integral part of the assessment of the critically ill neurological or neurosurgical patient. The advances in our understanding of neurological function and refinement in biochemical analysis there remains the

possibility of the usefulness of CSFs as diagnostic and prognostic markers in the future. New insights into the role of inflammation and the immune response in CNS infections have contributed to the development of new diagnostic strategies using markers of inflammation, and to the study of agents with focused immunomodulatory activity, which may lead to further adjunctive therapy in human disease.

REVIEW OF LITERATURE

Differential diagnosis between post-neurosurgical bacterial meningitis (PNBM) and aseptic meningitis is difficult. CSF lactate assay is proposed as a useful PNBM marker and its level is increased in that condition and is a better predictive marker than CSF hypoglycorrhachia or pleocytosis.⁽¹⁾ Among analytes measured in CSF such as D & L lactate, IL-6, IL-8, erythrocytes, leucocytes and protein, only D lactate level was found to be a useful marker for the differential diagnosis of Bacterial Meningitis (BM).⁽²⁾ Homovanillic acid (HVA) was found to be significantly higher in neonatal patients compared to controls and HVA abnormalities were also observed in many neurological disorders.⁽³⁾

A significant increase in plasma Neuron-Specific Enolase (NSE) and S-100 β protein levels were observed in spinal cord injuries.⁽⁴⁾ The other diagnostically useful markers in CSF include 14-3-3, S-100 β and NSE and elevated titers of these markers have been observed in neurodegenerative disorders. CSF analysis for 14-3-3, total tau and phosphorylated proteins using western blot technique in patients with various neurodegenerative disorders and in patients with Creutzfeldt-Jakob disease (CJD) showed positive 14-3-3 protein and elevated tau protein. A positive 14-3-3 protein band and increased t-tau proteins was noted in non-CJD group and Alzheimer's type (DAT) and in patients with cerebral vascular disease in acute phase and the p-/t-tau ratio was significantly higher in DAT patients compared to CJD patients.⁽⁵⁾ Generally CSF collected from meningitis patients are slightly xanthochromic and turbid. In meningitis, CSF protein, cholesterol, phosphorus, potassium and activities of aspartate aminotransferase (AST), Lactate Dehydrogenase (LDH), Creatinine Kinase – Total (CK-T) and total cell count were significantly increased while glucose and pH showed decrease suggesting that BM may have profound effects on blood and CSF parameters.⁽⁶⁾

CSF cholesterol and triglycerides are very useful analytes in the diagnosis of TM, pyogenic meningitis, viral encephalitis (VE) and hydrocephalus.⁽⁷⁾ In acute cerebrovascular accidents and in seizures, elevation of creatinine kinase BB (CK-BB) isoenzymes were

observed leading to prolonged alteration of consciousness. CK-T BB isoenzymes were also found to be elevated in patients with CNS infection, acute demyelinating disease, certain drug overdose, head trauma and in certain complex migraine.⁽⁸⁾ CK-BB immunoreactive isoenzymes were also significantly increased in newborns with neurologic disorders such as intra-ventricular hemorrhage, postasphyxial encephalopathy, CNS infections or persistent periventricular intra parenchymal echodensities than the normal newborns or those with sub arachnoid hemorrhage.⁽⁹⁾ Further, significant elevation in CSF total CK activity was observed in children with BM compared to children with either aseptic meningitis or normal suggesting that CSF total CK activity could be used to differentiate between bacterial and viral meningitis in situations where routine CSF analysis for other analytes are inconclusive.⁽¹⁰⁾

Among CSF enzymes, AST, LDH and CK-T are useful in the diagnosis of VE, AST and CK-T for TM and the level of CK-T in TM was significantly lower than that of VE. The myocardial enzymes of patients with cerebral functional disorder were significantly higher than those of patients with normal cerebral function. CNS infection is associated with myocardial injury with increased serum myocardial enzyme levels and hence serum levels of such myocardial enzymes should be measured in such patients.⁽¹¹⁾ CSF levels of CK, AST and LDH in VE patients are higher with a significant difference in CK-T and LDH and there was good correlation between CK-T, AST and LDH to the body temperature in VE children with pneumonia. In VE patients, CK-T, CK-MB, AST and LDH assays in CSF are used to diagnose myocardial injury in VE patients in the acute phase and convulsion will affect the level of the above enzymes.⁽¹²⁾

There was no significant differences in serum myocardial enzyme level between VE and TM. The CSF LDH level of TM group were prominently higher than those of VE. No correlations were found in CSF LDH level with serum myocardial enzyme level, with CSF leukocyte count and protein quantity. There is significant increase in the levels of serum myocardial enzyme and CSF LDH of adult patients with acute intracranial infection. The levels of serum myocardial enzymes and CSF LDH is helpful for the diagnosis and the differential diagnosis of intracranial infection in early stage.⁽¹³⁾ In earlier studies, the CSF LDH level of TM group were the highest, the purulent meningitis group were the next and VE showed the lowest. But significant differences between intracranial infection groups and normal control group were found. No correlations of CSF

LDH level with serum LDH were found. The CSF LDH level of adult patients with acute intracranial infection increases significantly and is a helpful parameter for the differential diagnosis of intracranial infection at early stage.⁽¹⁴⁾ LDH levels of the BM group was significantly higher than viral meningitis and there was no significant differences in serum LDH level among BM and viral meningitis. The CSF LDH level can be used for the differential diagnosis of BM and viral meningitis.⁽¹⁵⁾

Low sodium and chloride levels were observed in adults with acute intracranial infection depending on the type of bacterial infection. Measurement of serum potassium, sodium and chloride will be useful in the diagnosis of intracranial infection.⁽¹⁶⁾ Adenosine Deaminase (ADA) activity in CSF of the TM is significantly higher than that of the purulent meningitis. The activities of AST and LDH in CSF of the tubercular and purulent meningitis were higher than that of the viral meningitis. The level of total protein increased gently in viral meningitis, mildly in the TM and sharply in the purulent meningitis. CSF β 2-microglobulin and C Reactive Protein (CRP) levels in CSF of the three meningitis were found to be increased. The activities of AST and LDH in CSF is helpful for the diagnosis of BM, while ADA activity and protein level are helpful in the differential diagnosis of TM.⁽¹⁷⁾ CRP levels in serum and CSF of patients with purulent or TM were significantly higher than viral meningitis. CRP level in serum was found to be significantly different between purulent and TM and hence CRP in serum and CSF is a better marker for the differential diagnosis of intracranial infection.⁽¹⁸⁾ Serum sodium and chloride in tuberculous cephalitis were found to be less than that of purulent cephalitis. Serum calcium in purulent cephalitis and tuberculous cephalitis were within the subnormal range. The urea nitrogen in purulent cephalitis were found to be higher than that of viral and tuberculous cephalitis.⁽¹⁹⁾ The increase in serum tumor necrosis factor- α (TNF α), IL-6 and tumor necrosis factor receptor 1 (TNF-R1) levels were statistically significant at the onset of influenza virus-associated encephalopathy but the IL-6 level was found to be most useful for diagnosis. Serum IL-6 level may be the most useful indicator for the diagnosis and the clinical severity of influenza virus-associated encephalopathy.⁽²⁰⁾

The levels of IL-6 and TNF α in the VE group were also higher than those of the control. No significant relationship was found between elevations of CSF IL-6 and TNF α levels and CSF leukocyte counts. The determination of CSF IL-6 and TNF α levels may be valuable in distinguishing purulent meningitis from

viral meningitis and encephalitis. IL-6 and TNF α may contribute to the pathophysiological mechanisms of acute infection of the CNS.⁽²¹⁾

Oxidative stress plays an important role in the pathogenesis of demyelinating diseases, especially in multiple sclerosis (MS). Lipophilic anti oxidants in blood may induce negative impact on bioenergetics leading to neurodegenerative disorders.⁽²²⁾

CONCLUSION

This review article has highlighted the various biochemical tests which are useful for the differential diagnosis of diseases caused to CNS by many types of infections by bacteria and viruses. While biochemical tests in CSF like glucose, total protein, LDH, AST, CK-total, cholesterol, triglycerides, electrolytes and phosphate will help to diagnose varieties of disorders associated with CNS, additional special tests like CRP, D-lactate, CK-BB, Adenosine deaminase, IL-6, IL-8 and special protein S100 α , tau will help in all differential diagnosis of CNS disorders. This review article will be very useful for Neurologists and Clinical Biochemists to decide the appropriate biochemical tests based on clinical history.

Conflicts of Interest : The authors have no conflict of interest.

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