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RESEARCH ARTICLE

DIAGNOSTIC USEFULNESS OF ADENOSINE DEAMINASE IN BACTEREMIA

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ABSTRACT

Adenosine Deaminase (ADA) is an enzyme which is mainly involved in purine metabolism and is very much needed to breakdown Adenosine from food and maintain turnover of nucleic acid in tissues. Studies carried out in the past on the clinical usefulness of ADA has predicted its application in the diagnosis of variety of infectious diseases such as tuberculosis, typhoid, Infectious mononucleosis and certain malignancies especially those of haematopoietic origin. ADA levels in patients with pneumonia caused by *M.Pneumoniae* and *Chlamydia Spp* were found to be sensitive in diagnosing a particular type of infection. This review article summarises some important clinical usefulness of ADA measurement in body fluids.

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INTRODUCTION

Adenosine deaminase (ADA) is the most important key enzyme involved in the metabolism of Adenosine, one of the important base in the genetic material DNA. This enzyme is linked to several infectious diseases like Tuberculous meningitis, pneumonia and typhoid. Serum ADA activity probably reflects differences in cellular immune response to different infectious agents. The ADA determinations may give corroborative information on the etiologic agent of pneumonia (Klockars *et al*., 1991). The late onset of clinical symptoms and relatively benign clinical course in this patient emphasize the need to consider ADA deficiency in a broad spectrum of immunodeficient children (Levy *et al*., 1988). It is sometimes difficult to clinically diagnose mycoplasma pneumonia at an early stage before the rise of titer of antibody to Mycoplasma pneumoniae. Mycoplasma pneumonia may be related with T-lymphocyte activity, and its inflammatory process is different from that of bacterial pneumonia. ADA activity is a predominant T-lymphocyte enzyme, and its plasma activity is high in diseases in which cellular immunity is stimulated.

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Serum ADA activity in the group of mycoplasma pneumonia were higher than non-mycoplasma pneumonia, and that of normal control, suggesting that serum ADA activity in patients with acute pneumonia may be useful for the early diagnosis of mycoplasma pneumonia (Suga *et al*., 1989). Of the 20 mycoplasma pneumonia cases, 19 showed increased levels of ADA and in 17 of the 19, the increase of ADA was seen before the elevation of the specific antibody to Mycoplasma pneumoniae.

In contrast, serum ADA levels in all 20 cases of bacterial pneumonia were lower, indicating that assays for serum ADA and free IL-2 receptor levels are useful in distinguishing between bacterial and mycoplasma pneumonia at an early stage (Suga *et al*., 1991). ADA activity before inoculation was 25.6 IU/1, it reached 174.4 IU/1 on day 3 after inoculation of L. pneumophila. ADA activity returned to normal levels on day 14. ADA activity did not increase significantly in guinea pigs infected with the other types of bacteria. These findings suggest that measurement of plasma ADA activity may be useful for the diagnosis of Legionella infection (Nikaido *et al*., 1996). In some patients with atypical pneumonia (AP), ADA levels were significantly higher than in the previously related groups. Analysis within the group of atypical pneumonia showed significant differences for infections caused by

Coxiellaburnetii, Mycoplasma pneumonia and Legionella pneumophila, as compared with patients with bacterial pneumonia and normal control subjects. Serum ADA in patients with community-acquired pneumonia requiring hospitalization may provide useful additional diagnostic information on the aetiology of pulmonary infection (Molinos *et al*., 1997). ADA level of tuberculous group was above diagnostic cut-off, while only one sample was above cut-off in non-tuberculous group. The negative predictive value of ADA for the diagnosis of non-tuberculous etiology was 97.5% (39 of 40) lymphocytic pleural effusion patients and ADA levels in nontuberculous exudative pleural effusions rarely exceeded the cut-off set for tuberculous disease. The pleural fluid ADA levels were significantly higher in tuberculous exudative pleural effusions when compared with non-tuberculous exudative pleural effusions (Bharat (Kumar Gupta *et al*., 2010). ADA activity is a significant prognostic indicator for the development of constrictive pericarditis in tuberculous pericarditis (Komsuoglu *et al*., 1995).

The ADA1 (both ADA1m and ADA1c isoenzymes) was the major isoenzyme in the parainfective effusions with a median contribution of 70 percent. The ADA2 isoenzyme activity most likely reflects monocyte-macrophage turnover or activity, while ADA1 probably originates from lymphocytes or neutrophils. It is therefore essential to determine the isoenzyme profile when interpreting ADA activity levels in effusions. The measurement of the individual isoenzymes will enhance the diagnostic utility of ADA activity determinations in pleural effusions(Ungerer *et al*., 1994). Modulating endogenous adenosine was also effective in exacerbated 8-sulfophenyltheophylline ordiminished PNT tissue peroxidation. Survival from sepsis was also improved when PNT was used as a posttreatment. These data indicate that endogenous adenosine is an important modulatory component of systemic inflammatory response syndromes. These data also indicate that inhibition of ADA may be a novel and viable therapeutic approach to managing the systemic inflammatory response syndrome without ablating important physiological functions (Adanin *et al*., 2002).

Adenosine was used to survive under extremely acidic conditions via the production of NH(3). It has been proposed that amino acid decarboxylation is the major system for the resistance of E. coli to acidic stress. ADA deamination was shown to induce the survival under acidic conditions, demonstrating that bacteria have alternative strategies to survive under acidic conditions besides amino acid decarboxylation (Sun *et al*., 2012). The partially purified ADA is labile to a number of environmental conditions, particularly to phosphate buffers of pH 6.8 or less. A disproportionately slow rate of adenine deamination by cells utilizing lactate permits a more prolonged period of induction and, consequently, a greater quantity of enzyme to be synthesized; cell division, but not enzyme inactivation, reduces enzyme concentration. The ADA's of Aerobacteraerogenes and Salmonella typhimurium are not inducible (Charles N. Remy *et al*., 1968). Compared with the spontaneous bacterial peritonitis (SBP) group, the tuberculous peritonitis (TBP) group had significantly higher ascitic protein, ADA and lactate dehydrogenase (LDH) levels.

Levels of proteins ADA & LDH in Ascitic fluid may help to differentiate TBP & SBP groups (Hai-jun Huang *et al*., 2014). ADA activity was significantly higher in the typhoid fever group. Untreated typhoid fever patients had their higher ADA activity between 10th and 15th day of illness. When ADA cut point was set at 80 U/I, sensitivity of the test was 91.8% and specificity was 91.4% as a preliminary clue to the recognition of typhoid fever (Casanueva *et al*., 1991). The medium serum ADA values were significantly higher in children with typhoid fever ($P < 0.0001$) in relation to the values in the control group. This test had a sensitivity of 91.9% and a specificity of 92.5% in identifying the patient with typhoid fever when using 80 units/liter as the cutoff values. The positive predictive value of the test was 83.8% and the negative predictive value was 96%. Determination of ADA values in serum could be helpful in the early diagnosis of typhoid fever (Vasanueva *et al*., 1992). ADA levels in serum were higher in TB compared to non-TB groups. Using a cut off of 35 IU/L, the sensitivity and specificity of Pleural Fluid ADA (PF-ADA) in the diagnosis of TB was computed to be 83.3% and 66.6% respectively. At a cut-off level of 100 IU/L, PF-ADA was found to have a sensitivity 40% and specificity 100%. From this study it is concluded that, using 100 IU/L as the cut-off, it is possible to avoid pleural biopsy to ascertain the diagnosis of TB in as much as 40% of the patients (Sharma *et al*., 2001).

Some studies suggest significant increase in serum ADA and ADA-2 values, which decreased during the first 2 months in the patients as a whole, followed by stabilization of ADA activity. This decline was mainly due to marked decrease in ADA2. The ratio of ADA(2)/ADA was found to be better indicator of tuberculosis. Lymphocyte neutrophil ratio (L/N) > 0.69 gave additional benefit to increase the sensitivity and specificity for the use of ADA as marker in diagnosing tuberculosis (Salman, 2003). The combined use of activity of ADA, its isoenzymes and total and differential cell counts is a better indicator and gives better understanding to diagnose and evaluate tuberculosis and response to therapy. The PF-ADA levels were significantly higher in different types of exudative effusions than in transudates. An ADA level < 40 IU x L(-1) virtually excluded a diagnosis of tuberculosis in lymphocytic pleural effusions. Adenosine deaminase1/adenosine deaminase (p) correctly classified all nontuberculous lymphocytic pleural effusions with high adenosine deaminase levels (Jimenez *et al*., 2003).

The ADA level in TBM cases had significant correlation with CSF cell count ($P<0.01$), lymphocyte percentage ($P<0.02$) and protein concentration ($P<0.02$). Thus, the CSF ADA activity assay was found to be a simple, useful and rapid diagnostic test for the early recognition of TBM in children (Mishra *et al*., 1996). Serum ADA activity with high specificity percentage may be a useful alternative test in restricted resource areas to rule out diagnosis of Pulmonary Tuberculosis (PTB). However, serum ADA activity is not a useful tool for TB diagnosis (Shokrollah *et al*., 2015). Lowering adenosine and 2′-deoxyadenosine levels using ADA enzyme therapy decreased the pulmonary eosinophilia and resolved many of the lung histopathologies. In addition, genetically restoring ADA to the forestomach of otherwise ADA-deficient mice prevented adenine metabolic disturbances as well as lung

inflammation and damage. These data suggest that disturbances in purinergic signaling mediate the lung inflammation and damage seen in ADA-deficient mice (Micheal Blackburn *et al*., 2000). To distinguish pleural TB, pleural levels of ADA-2 have the highest sensitivity among the different diagnostic parameters and may find a place as routine investigation for early detection of TB in the future (Sibel Yurt *et al*., 2014). Measurement of serum ADA level do not have enough sensitivity to assist in the diagnoses of tuberculosis patients from other respiratory diseases and not evaluated perform well enough to replace sputum smear microscopy. Thus, this tests have little role in the diagnosis of PTM (AliasgharFarazi *et al*., 2010). ADA estimation in CSF is not only simple, inexpensive and rapid but also fairly specific method for making a diagnosis of tuberculous etiology in TBM, especially when there is a dilemma of differentiating the tuberculous etiology from non-tuberculous ones. For this reason ADA estimation in TBM may find a place as a routine investigation (Bharat kumar Gupta *et al*., 2010).

Even with lower ADA activity in ascites among cirrhotic patients, ADA values were significantly elevated during Tuberculous peritonitis, indicating that ADA can still be a valuable diagnostic tool (Yi-Jun Liao *et al*., 2012). IFN-γ and ADA could be used as valuable parameters for the differentiation of tuberculous from non-tuberculous effusion, and IFN-γ was more sensitive and specific for tuberculous effusion than ADA (Fahmi Yousef knan *et al*., 2013). ADA remains useful for the diagnosis of TPE even in low-to-intermediate prevalence scenarios when combined with the lymphocyte proportion (Alberto Garcia *et al*., 2012). Infections with intracellular bacteria such as chlamydiae affect the majority of the world population. Infected tissue inflammation and granuloma formation help contain the short-term expansion of the invading pathogen, leading also to local tissue damage and hypoxia. However, the effects of key aspects of damaged inflamed tissues and hypoxia on continued infection with intracellular bacteria remains unknown. The ADA and QFT-G assays might be used to rapidly diagnose TB peritonitis and initiate prompt treatment while waiting for a final diagnosis using the standard culture approach.(Matthew *et al*., 2009) The inhibition of ADA by Erythro-9-(2-hydroxy-3-nonyl)-adenine can prevent *Clostridium difficile* Tx A-induced damage and inflammation possibly through the A_{2A} adenosine receptor, suggesting that the modulation of adenosine/ adenosine deaminase represents an important tool in the management of C. difficile-induced disease (Ana Flavia *et al*., 2011).

Conclusion

This review article has brought out some important clinical usefulness of measuring ADA in serum, effusion fluids and CSF. ADA activities in serum are very useful in distinguishing bacterial and mycoplasma pneumonia and are a valuable prognostic marker for TBM in children. Its measurement is very helpful in the early diagnosis of typhoid fever. ADA levels in CSF are now emerging as a valuable marker for the diagnosis of TBM in children. ADA iosenzymes and its ratio are now being utilised on a large scale for diagnosis. Future research should be directed to clearly embark a solid lab investigation protocol for the measurement of ADA in a fixed type of biological sample for the differential diagnosis of all bacterial infections.

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