Serum ADA Levels and LDH Levels in Tubercular Meningitis in Paediatric Patients

Gonella Geetha Meenakshi[1]

ABSTRACT

Introdction: Fall in the physiologic concentration of glucose in the cerebrospinal fluid (CSF) is the most common finding observed in patients with tuberculous meningitis (TM) and bacterial meningitis. In back 1980, for the first time, alteration in the lactate concentrations was detected in the CSF of the patients with TM. Hence; we evaluated the levels of adenosine deaminase (AD) and LD in paediatric patients with TM having adverse neurological outcome and compared it with the levels in TM patients without adverse outcome.

Material and Methods: The present study included all the paediatric patients that were admitted to the ward with the chief problem of TM. TM cases were further staged with severity following the classification of British Medical Research Council classification. CSF LD and CSF AD were measured in all the cases of TM by standard photometric assays and Berthelot method respectively. All the results were assessed and analyzed by SPSS software. Student t test and chi-square test was used for the assessment of level of significance.

Results: As far as staging of the disease is concerned, patients with TM group with adverse outcome, the mean staging was 2.8 while in the other group, the mean staging of the patients was 1.8. Non-significant results were obtained while comparing the demographic details of the patients in the two study groups. However, as far as staging of the disease is concerned, significant difference was observed in between the two study groups. Mean AD level in the patients of TM with adverse outcome and in patients without adverse outcome was 17.5 and 11.5 IU/L respectively. When evaluating the mean LD level among patients with and without adverse outcome, the value was observed to be 40.8 and 33.9 IU/L respectively. Significant difference was observed while comparing the mean value of AD level among patients of the two study groups.

Conclusion: Further substantial evidences are required for standardizing the CSF AD and LD levels as diagnostic and prognostic markers in diagnosing the cases of TM.

Keywords: Adenosine Deaminase, Lactate Dehydrogenase, Meningitis

INTRODUCTION

One of the most severe complication of tuberculosis manifesting in extrapulmonary sites is the Tuberculous meningitis (TM). In approximately 80 percent of the cases, it occurs in children of nearly 5 years of age. Increase in availability of vaccinations had led to the declining in the prevalence of bacterial meningitis. However, in cases of childhood meningitis, one of the treatable and preventable causes of death is Mycobacterium tuberculosis.[1] Overall risk of death due to neurological complication in children with TM has been reported to be approximately 20 percent.[2] Sites of TM infection are in direct contact with cerebrospinal fluid (CSF). A healthy amount of information is contained in CSF regarding the diagnosis of TM.[3] A predominance of leukocytes with increase in protein contents have been observed in the CSF of TM cases.[4] In the recent past, although very complex, the estimation of levels of the lactate and the alteration occurring in its physiologic levels have been utilized for the differentiation and as an early predictor marker for the differential diagnosis of bacterial meningitis and aseptic meningitis.[5,6] Measurement of levels of Lactate dehydrogenase (LD) has been measured first of all approximately 60 years back. Although occasionally performed, the alteration in the levels of LD has been used as a marker for predicting the occurrence of bacterial meninigits.[7,8] Hence; we evaluated the levels of adenosine deaminase (AD) and LD in paediatric patients with TM having adverse neurological outcome and compared it with the levels in TM patients without adverse outcome.

MATERIAL AND METHODS

The present study was conducted in the department of paediatric medicine and biochemistry of the Osmania general hospital, Hyderabad and included all the paediatric patients that were admitted to the ward with the chief problem of meningitis from June 2013 to July 2015. Ethical approval was taken from the institutional ethical committee and written consent was obtained after explaining in detail the entire research protocol. The guidelines of the Consensus Statement of Indian Academy of Paediatrics Working Group was taken as standard for making the final diagnosis of TM.[9] All other paediatric patients with the diagnosis of any other type of meningitis were excluded from the present study. TM cases were further staged with severity following the classification of British Medical Research Council classification.[10] Following parameters were used for classifying the TM cases as affected by neurological manifestation and adverse effects:

- Permanent neurological deficit
- Hydrocephalus
- Death

Measurement of the following parameters was done in the cases of TM:

- CSF LD
- AD

For the measurement of the LD, standard photometric assays

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was used while Berthelot method was used for the assessment and evaluation of CSF AD levels.[11] Complete demographic details of the patients in the two study groups were also recorded and compared.

STATISTICAL ANALYSIS

All the results were assessed and analyzed by SPSS software. Student t test and chi-square test were used for the assessment of level of significance. P-value of less than 0.05 was taken as significant.

RESULTS

Figure 1 highlights the demographic details of the patients in the two study groups. Mean age of the patients in TM group with adverse outcome and without adverse outcome was 5.3 years and 5.4 years respectively. In TM group with adverse outcome, 33.3 percent of the total patients were males while in the other group, 68.7 percent of the patients were females. As far as staging of the disease is concerned, patients in TM group with adverse outcome, the mean staging was 2.8 while in the other group, the mean staging of the patients was 1.8. Table 1 shows the p-value for the demographic and clinical parameters. Non-significant results were obtained while comparing the demographic details of the patients in the two study groups. However, as far as staging of the disease is concerned, significant difference was observed in between the two study groups. Figure 2 highlights the various CSF parameters for the patients in the two study groups. Mean AD level in the patients of TM with adverse outcome and in patients without adverse outcome was 17.5 and 11.5 IU/L respectively. When evaluating the mean LD level among patients with and without adverse outcome, the value was observed to be 40.8 and 33.9 IU/L respectively. Table 2 shows the p-value for various CSF parameters. Significant difference was observed while comparing the mean value of AD level among patients of the two study groups.

DISCUSSION

One of the most commonly affecting pathologic forms of tuberculosis affecting the central nervous system (CNS) is the TM.[12] Among all extra-pulmonary tuberculosis cases, CNS pathologies accounts for only 5 percent of it and in children, the peak age of incidence of occurrence of TM is less than four years.[13] However; as a result of increase in cases of HIV positive patients, a rise in the number of cases of TM in adults have been observed. Subacute meningitic illness forms the classical presentation of TM which cannot be differentiated form the other types of meningitis very easily solely on the basis of clinical feature. However, the diagnosis can be partially visible only when the disease has advanced to a higher stage but by that time, the prognosis of the diseases becomes very poor. British Medical Research Council has staged the disease according to the varying severity.[10] The enzyme which acts as a catalyst in the purine salvage pathways that helps in the conversion of adenosine and deoxyadenosine to inosine and deoxyinosine

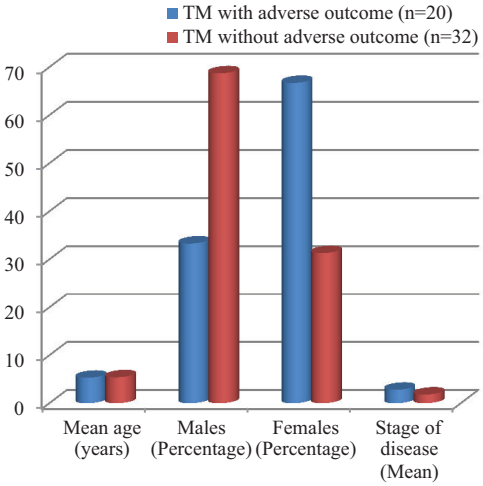

Figure-1: Demographic and clinical parameters

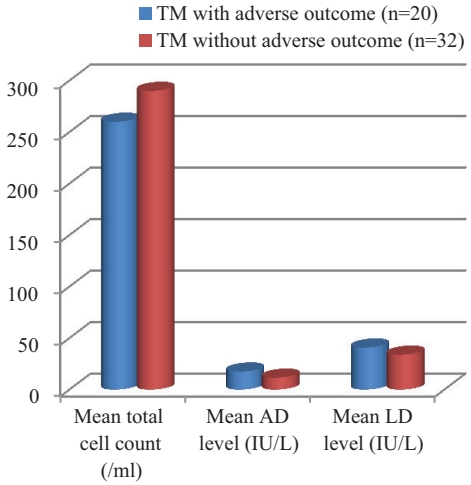

Figure-2: CSF parameters for patients in both the study groups

Parameter		TM with adverse outcome (n=20)	TM without adverse outcome (n=32)	p-value
Mean age (years)		5.3	5.4	0.41
Sex	Males (Percentage)	33.3	68.7	0.51
	Females (Percentage)	66.7	31.3	
Stage of disease (Mean)		2.8	1.8	0.01*
*Significant				

Table-1: p-value for the demographic and clinical parameters

CSF Parameter	TM with adverse outcome (n=20)	TM without adverse outcome (n=32)	p-value
Mean total cell count (/ml)	260	290	0.41
Mean AD level (IU/L)	17.5	11.5	0.01*
Mean LD level (IU/L)	40.8	33.9	0.81
*: Significant			

Table-2: p-value for various CSF parameters

respectively is the AD.[14] as the mitogenic potential and antigenic responses of lymphocytes increases, so is the increase in the activity of AD enzyme is seen.[15] Analysis of routine CSF fluid parameters is done in cases of cerebral pathologies. However, additional biochemical parameters have also shown to be of significant importance in predicting the confirm diagnosis of TM. One such parameter is LD.[16] Hence; we evaluated the levels of adenosine deaminase (AD) and LD in paediatric patients with TM having adverse neurological outcome and compared it with the levels in TM patients without adverse outcome.

In the present study, we observed that staging of the disease significantly differed in the two study groups with higher stage of disease observed in TM cases associated with adverse neuropathic outcome (Figure 1, Table 1). It can be presented in a way that patient with higher staging is associated with more adverse neuropathic effects. Donald et al evaluated the mean level of cerebrospinal fluid (CSF) lactate and LD in patients with TM and differentiated it from aseptic meningitis. More than 90 percent of the cases of TM were detected by using the upper limit of normal physiologic values of CSF lactate that were 275mmol/l giving a sensitivity score of 92 percent. 21 out of 38 cases were detected as TM by using the upper limit values of CSF lactate as 385 mol/l which gave a total sensitivity score of less than 70 percent. Conventional chemical analysis method could be superseded by both the tests in differentiating TM from other type of meningitis.[17] Donald et al investigated the value of CSF lactate and LD in patients with meningitis to assess whether these parameters help in differentiating aseptic meningitis from bacterial meningitis. They assessed and divided all the patients broadly into three main groups. One comprised of control group in which patients without meningitis were included. Second group included patients affected by aseptic meningitis while the third group included patients that were affected by bacterial meningitis. They observed that in comparison with the conventional chemical investigation methods, the sensitivity of these tests was higher in detection of meningitis. From the results, they concluded that as in the case of conventional chemical methods, normal physiological values might be given by both the investigatory tests.[18] Mdaghri et al assessed the lactic acid levels in CSF with the help of enzymatic test in more than 150 patients. 300 mg/l was used as the upper limit of the CSF lactate. From the results, they observed that in the diagnosis and differential diagnosis of pyogenic meningitis and tuberculous meningitis cases in partially treated states, CSF lactate levels are quite useful. However, accordingly, clinical correlation is also necessary for confirming the diagnosis as increase in CSF lactate levels is very non-specific.[19] Tang et al evaluated in CSF lactate levels in twenty one patients with final confirmed diagnosis of tuberculous meningitis. They observed a uniform elevation in the CSF lactate levels greater than 3.9mmol/l. However, no correlation was observed regarding the clinical staging and prognosis of the cases with the amount of rise in CSF lactate concentration. From the results, they concluded that despite adequate antitubercular therapy, a constant elevation of the CSF lactate levels has been observed in the early stage of illness.[20] Donald et al simultaneously evaluated the CSF and plasma adenosine deaminase (ADA) activity in patients with tuberculous meningitis and assessed the diagnostic role of these biochemical parameters in making the diagnosis of tuberculous meningitis. They analyzed and divided all the patients into four prominent groups. First group comprised of 174 patients in which non meningitis was detected. Second group comprised of 40 paediatric patients which were suffering from aseptic meningitis. The third group consisted of 31 paediatric patients in which bacterial meningitis was confirmed while the fourth group comprised of 27 paediatric patients in which tuberculous meningitis was detected. Determination of CSF ADA was done in 23, 19 and 13 paediatric patients with aseptic meningitis, bacterial meningitis and tuberculous meningitis respectively. They observed a rise in the levels of CSF/ADA ratio and absolute CSF ADA activity in patients with tuberculous meningitis and bacterial meningitis. However, no elevation in the levels of these parameters was seen in cases of aseptic meningitis and no-meningitis group. From the results, they concluded that both these biochemical parameters can be used in distinguishing tuberculous meningitis from aseptic meningitis.[21] Knight et al reviewed the data on lactate and lactate dehydrogenase values and their role in various types of meningitis. They concluded that as the early predictors of bacterial meningitis, these biochemical parameters are more sensitive in comparison with glucose levels and further, they also help in distinguishing the cases of tuberculous meningitis from aseptic meningitis. However, when compared in between these two parameters, in certain cases, sensitivity of lactate dehydrogenase was observed to more than that of lactate.[22] From the past few decades, it has been a diagnostic challenge to confirm the diagnosis of TM through clinical parameters alone. It is necessary to evaluate biochemical parameters for sorting the list of differential diagnosis and finalizing the provisional diagnosis. In the CNS, many of the enzymes are present in abundance. However; the blood-brain barrier is disturbed in cases of meningitis. It results in increases in activity of certain CSF enzymes. These results have been used by various authors in the past for detecting the change in values of various biochemical enzymes to correlate with the prognosis and severity of the meningitis. However, future research is required for authenticating the use of these CSF enzymes in predicting the severity and prognosis of the diseases.[23-26] Dhawan et al evaluated the long-term outcome of paediatric tuberculous meningitis treated with modern 4-drug antitubercular therapy. From the results, they concluded that remarkable improvement is shown by the survivors despite the high hospital motility rate.[27] Israni et al assessed the clinic-pathologic and radiographic profile of the paediatric TM. From the results, they concluded that the most adverse prognostic factor seen is the raised intra-cranial pressure.[28] Rios-Sarabia N et al and others assessed the TM cases with clinical and laboratory parameters. From the results, they concluded that for the rapid diagnosis of TM, CSF assessment with PCR is a very reliable method.[29,30]

CONCLUSION

From the results, the authors conclude that further substantial evidences are required for standardizing the CSF AD and LD levels as diagnostic and prognostic markers in diagnosing the cases of TM.

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