A STUDY OF CREATINE PHOSPHOKINASE LEVELS IN CEREBROSPINAL FLUID AND SERUM IN PATIENTS OF PYOGENIC AND TUBERCULAR MENINGITIS

Ankur *, Rampure M Dilip **, Irshad Hussain Askari ***

***** Associate professor, Department of Physiology, MNR Medical College & Hospital, Sangareddy 502294, Telangana, India. **Professor and HOD, Department of Medicine, *** Professor and HOD, Department of Physiology. MNR Medical College & Hospital, Sangareddy 502294, Telangana, India.

Background & objective: Creatine phosphokinase was measured serially in cerebrospinal fluid (CSF) and serum in forty patients, twenty each of pyogenic and tubercular meningitis. Twenty healthy cases act as control. The aim of the study is to find whether creatine phosphokinase levels has any diagnostic or prognostic significance in serum and C.S.F in cases of pyogenic and tubercular meningitis. **Material and method:** The enzymatic activity was measured serially on (1^{st}, 3^{rd} and 5^{th} day) in cases of pyogenic meningitis and (1^{st}, 3^{rd}, 7^{th} and 14^{th} day) in tubercular meningitis. The clinical details including the level of consciousness, neurological deficit and mortality were correlated with the enzymatic activity and prognosis. **Results:** In pyogenic meningitis creatine phosphokinase activity in C.S.F. was raised on 1^{st} day as comparison to tubercular meningitis it was on 3^{rd} day of admission and progressively dropped to significantly lower values with the recovery of the patient. Definite correlation was demonstrated between the enzyme activity in C.S.F. and level of consciousness, mortality in cases of tubercular and pyogenic meningitis. **Conclusion**: Creatine phosphokinase activity in cerebrospinal fluid has a diagnostic and prognostic value in patients of pyogenic and tubercular meningitis.

Keywords: Cerebrospinal fluid, Creatine phosphokinase, tubercular meningitis, pyogenic meningitis.

Author for correspondence: Dr. Ankur. M.B.B.S, M.D Physiology, Associate Professor Department of Physiology. MNR Medical College & Hospital, Sangareddy, 502294, Telangana India. Telephone No. : 00918106983131. E-mail: ankurwadhwa.dr@gmail.com

Introduction:

Meningitis is inflammation of the meninges that cover the brain and spinal cord. Meningitis disturbs the blood brain barrier (BBB) and is expected to cause rise in enzymatic activity[1]. The estimation of tissue enzymes released into body fluids as the result of pathological processes often serves to indicate the presence of disease and in some cases the serial determination of enzyme activity aids in assessing patient's clinical course. Creatine phosphokinase is one such tissue enzyme which has found its great utility in the diagnosis of myocardial infarction[2], various muscle diseases[3] and in various neurological disorders[4]. Tubercular and pyogenic meningitis are common neurological disorders, in most cases the diagnosis can be made by a well taken clinical history and carefully performed physical examination supplemented by routine cerebrospinal fluid examination. In some cases like partially treated pyogenic meningitis the diagnostic challenge become perplexing, more so in the absence of characteristic cellular and biochemical changes in cerebrospinal fluid (C.S.F.). The variability of the clinical picture of tubercular and pyogenic meningitis also makes it difficult to comment on the prognosis of the disease in the initial stages. The present study was carried out in patients of pyogenic and tubercular meningitis First to find out whether creatine phosphokinase estimation in serum and C.S.F. has any diagnostic or prognostic significance. Second to see whether there is any relationship between levels of serum and C.S.F. creatine phosphokinase.

Material and Methods:

This study was carried out on 60 subjects, 20 each of pyogenic and tubercular meningitis and 20 healthy cases, acting as control. The cases were admitted in Mamata general hospital. Cases having associated diseases like myopathy, polymyositis, dermatomyosisits, muscular dystrophy, cerebrovascular accidents, trauma, head injury, ischemic heart disease and hypothyroidism were excluded from the study. The 20 control were the patients admitted in surgical wards for elective surgery, under spinal anesthesia and C.S.F. samples were taken at that time. Only those cases were selected for the purpose of control who had no neurological disorder or any other disease likely to have effect on CPK estimation. C.S.F. was collected under all sterile precautions, lumber puncture was done on the admission day, 3^{rd} day and 5^{th} day in cases of pyogenic meningitis and in cases of

tubercular meningitis on the admission day, 3rd day 7th day and 14th day of admission. 5 ml of blood were collected by venipuncture for the enzyme study on the same days and at the same time when C.S.F. collection was done. The enzyme activity in serum and C.S.F. was estimated immediately after collection, wherever impracticable the specimens were stored in a refrigerator for not longer than 24 hours and then analyzed[5]. All selected subjects underwent detailed neurological examination with special reference to altered level of consciousness, degree of neurological deficit and signs of meningeal irritation were recorded. The blood sample was collected on the day of admission for estimation of routine and biochemical investigation like complete haemogram, random blood sugar (RBS), serum urea, serum creatinine, liver function test (LFT), electrolyte, urine routine and microscopy. Chest X-ray PA view done in all cases. The diagnosis of pyogenic meningitis and tubercular meningitis was based on biochemical, microscopic examination, relevant staining and culture of the CSF for bacteria, mycobacterium tuberculosis. CSF examination was diagnostic in all cases and only the cases with definitive diagnosis of pyogenic meningitis or tubercular meningitis were included. The diagnosis of tubercular meningitis was made with CSF low sugar, elevated proteins with lymphocytic pleocytosis and positive evidence of mycobacterium tuberculosis either on CSF Ziehl-Neelsen staining or culture and/or PCR. All cases of pyogenic meningitis had CSF low sugar with evidence of neutrophilic pleocytosis, raised protein and positive evidence the bacteria on Gram's staining or culture and sensitivity. Statistical analysis was done by applying student 't' test. For the comparison of various results within the same group, on different days of hospitalization, the paired 't' test was applied, whereas for the comparison between the two groups of pyogenic meningitis or tubercular meningitis versus control subjects; unpaired 't' test was applied.

Result:

Serum and C.S.F. was studied for activity of C.P.K. in a total 60 cases. Of these 20 cases served as control while the remaining 40 patients were divided into two groups of 20 each. One group consisted of patients suffering from pyogenic meningitis and the other group, of the patients suffering from tubercular meningitis.

Table 1: Age and Sex distribution of cases.

	Cases	Number	Male	Female	Age Range	Mean
1	C.G	20	8 (40%)	12 (60%)	32-37 years	34.15
2	P.M	20	11 (55%)	9 (45%)	16-38 years	21.4
3	T.M	20	12 (60%)	8 (40%)	14-40 years	30.9

C.G: Control Group, P.M: Pyogenic Meningitis, T.M: Tubercular Meningitis.

Table 2: Comparison of Serum CPK activity and CPK activity in C.S.F. between control group and cases of pyogenic meningitis.

Group	No. of Cases	CPK range	Mean ± SD	P
Serum CPK activity				
Control	20	5-48	18.2 ± 9.99	
1st Day	20	6-72	22.65 ± 14.35	>0.05
3rd Day	19	15-58	26.89 ± 16.53	>0.05
5th Day	19	8-62	22.73 ± 11.39	>0.05
CPK activity in C.S.F.				
Control	20	0-11	4.1 ± 2.73	
1st Day	20	0-191	49.30 ± 40.76	<0.01
3rd Day	19	6-98	30.21 ± 26.23	<0.01
5th Day	19	4-101	24.10 ± 23.50	<0.01

Table 3: Comparison of CPK activity in Serum and CPK activity in C.S.F. between control group and cases of Tubercular meningitis.

Group	No. of Cases	CPK Range	Mean ± SD	P
Serum CPK activity				
Control	20	5-48	18.2 ± 9.99	
1st Day	20	4-89	26.80 ± 20.56	>0.05
3rd Day	20	8-58	20.7 ± 11.6	>0.05
7th Day	18	6-38	20.55 ± 9.10	>0.05
14th Day	18	7-30	15.05 ± 5.03	>0.05
CPK activity in C.S.F.				
Control	20	0-11	4.1 ± 2.73	
1st Day	20	4-47	19.1 ± 12.28	<0.01
3rd Day	20	11-69	27.35 ± 16.01	<0.01
7th Day	18	4-71	14.27 ± 8.35	<0.01
14th Day	18	4-32	9.55 ± 6.75	<0.01

Table 4: Level of consciousness, neurological deficit and mortality among the cases of Pyogenic Meningitis.

Group	No. of Cases	Serum CPK Mean ± SD	p	C.S.F CPK Mean ± SD	P
Level of Consciousness					
Fully Conscious	9	24.33 ± 19.33	>0.05	22.00 ± 19.6	>0.05
Semi Conscious	6	25.00 ± 9.77	>0.05	48.00 ± 10.89	<0.01
Unconscious	5	16.80 ± 8.31	>0.05	100.00 ± 51.80	<0.01
Neurological Deficit					
Patients with Neurological deficit	2	21.50 ± 14.8	>0.05	32.00 ± 12.72	>0.05
Patients without Neurological deficit	18	22.77 ± 14.7		51.22 ± 42.52	
Mortality					
Survived patients	18	22.62 ± 15.07	>0.05	40.11 ± 23.52	<0.01
Expired patients	02	23.00 ± 7.07		132.00 ± 83.43	

Table 5: Level of consciousness, neurological deficit and mortality among the cases of Tubercular Meningitis.

Group	No. of Cases	Serum CPK Mean ± SD	p	C.S.F CPK Mean ± SD	P
Level of Consciousness					
Fully Conscious	7	25.28 ± 11.9	>0.05	7.28 ± 3.19	>0.05
Semi Conscious	8	25.25 ± 26.86	>0.05	19.5 ± 5.75	<0.01
Unconscious	5	31.4 ± 22.2	>0.05	35.00 ± 9.11	<0.01
Neurological Deficit					
Patients with Neurological deficit	3	13.00 ± 7.9	>0.05	14.00 ± 8.00	>0.05
Patients without Neurological deficit	17	29.23 ± 21.26		20.00 ± 12.86	
Mortality					
Survived patients	17	25.76 ±		15.35 ±	

		19.0	>0.05	8.51	<0.01
Expired patients	3	32.66 ± 32.5		40.33 ± 7.63	

Discussion:

The present study was done in 40 patients, 20 each of pyogenic and tubercular meningitis. 20 patients served as control. Table 2 the C.P.K. activity in serum in the control group was 5 to 48 IU/L[6]. The C.P.K. activity in C.S.F. in the control group was 0 to 11 IU/L[6]. In 20% of cases there was no detectable C.P.K. activity. Undetectable enzyme activity in C.S.F. in control cases has also been reported by other authors[7]. In our study C.P.K. was raised in 5% of cases on 1st day, 21% on the 3rd day, and 5% on the 5th day in cases of pyogenic meningitis. The range of activity of serum C.P.K. on 1st day, 3rd day and 5th day was 6 to 72 IU/L, 15 to 58 IU/L, 8 to 62 IU/L respectively. When compared with control group no statistical significance was seen[8]. C.P.K. activity in C.S.F. was raised in 90% of cases on 1st day, 73% on the 3rd day and 53% on 5th day in pyogenic meningitis. On comparison with the control group it was highly statistically significant[8]. In the present study 10% of cases on the 1st day, 5% on the 3rd day had raised serum CPK activity in tubercular meningitis, while none of the patients showed raised serum CPK activity on 7th and 14th day of admission. As per Table 3 the range of CPK activity in serum in tubercular meningitis on the 1st day, 3rd day, 7th day and 14th day of admission was 4 to 89 IU/L, 8 to 58 IU/L, 6 to 38 IU/L and 7 to 30 IU/L respectively. When compared to the enzyme activity in the control group, no statistical significance could be demonstrated[9]. In case of CPK activity in C.S.F. in tubercular meningitis 60% of cases on the 1st day of admission had raised activity in C.S.F., while as on the 3rd, 7th and 14th day of admission 90%, 33% and 16% had raised CPK activity in C.S.F. respectively. The range of CPK activity in C.S.F. observed was 4 to 47 IU/L, 11 to 69 IU/L, 4 to 71 IU/L and 4 to 32IU/L on the admission day 3rd day, 7th day, and 14th day respectively. When compared to the C.S.F. enzyme activity in the control group the values were highly significant statistically. In present study we observed that CPK activity in C.S.F. in tubercular meningitis was highest on the 3rd day of admission and dropped to lower levels on the 14th day as the patient recovers[9].

As per Table 4 out of 20 cases of pyogenic meningitis 9 were full conscious or drowsy, 6 were semi-conscious and 5 were unconscious. Two cases had neurological deficit at the time of presentation, one had bilateral facial nerve palsy and the other had unilateral facial nerve palsy, of these 2 cases the former was semi-conscious at the time of presentation and the latter was drowsy. Two patients of pyogenic meningitis died in our study, one on the 2nd day and other on the 6th day of admission. Both the patients who expired were unconscious at the time of admission. The recovery in rest of 18 patients was uneventful. The patient with bilateral facial nerve palsy was having mild weakness of facial muscles at the time of discharge and the other recovered his facial weakness by the 10th day of admission. The CPK activity in the serum did not have any correlation with the presenting levels of consciousness in cases of pyogenic meningitis. When the average serum CPK activity compared with control (18.2±9.99 IU/L) showed no statistical significant ($p>0.05$), even compared together the values had no statistical significant ($p>0.05$). In contrast to the CPK activity in serum the enzyme activity in C.S.F. had definite correlation with the level of consciousness in patients of pyogenic meningitis. The CPK activity in C.S.F. was significantly high in unconscious group (100±51.80 IU/L) and semi-conscious (48.00±10.89 IU/L) in comparison to conscious or drowsy patients (22.00±19.6IU/L), the values being highly significant statistically ($p<0.01$)[10].

Out of 2 patients who expired one had initial serum CPK activity of 18 IU/L and the other 28 IU/L. The former died on the 6th day and the latter on the 2nd day of admission. Both were unconscious at the time of admission. The patient who died on the 6th day of admission showed a rise of serum CPK activity on the 3rd day (58 IU/L) and 5th day (62 IU/L) of admission. However, the comparison of initial CPK activity in serum in the expired patients (23.00±7.07IU/L) was of no statistical significance ($p>0.05$) when compared with survived patients or with the control group. The initial enzyme activity in C.S.F. in these two patients was significantly high (132.00±83.43 IU/L) compared to the patients who survived (40.11±23.52 IU/L). The patients who

expired on the 6th day of admission showed CPK activity of 101 IU/L in C.S.F. on the 5th day of admission. The interesting point we observed was that other 3 unconscious patients of pyogenic meningitis who recovered had also raised initial CPK activity in C.S.F. but the enzyme activity receeded markedly by the 5th day of abmission[10].

Table 5 shows that out of 20 cases of tubercular meningitis 7 were fully conscious or drowsy, 8 were semi-conscious and 5 were unconscious at the time of presentation. 3 out of 20 patients had neurological deficit at the time of admission in the form of cranial nerve palsies. The neurological deficits observed in these cases was right sided 3rd and 6th nerve involvement in one patient, bilateral 3rd, 6th and 7th cranial nerve involvement in the 2nd and the 3rd patient had left 7th cranial nerve palsy; the first two were semi-conscious and the third patient was drowsy. All the three patients recovered from the neurological deficit by the 3rd week of admission. Three patients of tubercular meningitis expired, two on the 4th day of admission and the third on the 26th day of admission, of the three patients who expired, two were unconscious at the time of admission and the third one who died on the 26th day of admission was semi-conscious at the time of admission.

Serum CPK activity did not reveal any correlation with the presenting level of consciousness, when compared among each other and the control group the values were insignificant statistically ($p>0.05$). In contrast to the CPK activity in serum the enzyme activity in C.S.F. was significantly high in unconscious group (36.00±9.11 IU/L) and semi-conscious group (19.5±5.75 IU/L) when compared to fully conscious or drowsy group of patients (7.28±31.9 IU/L)[10].

Of the 20 patients of tubercular meningitis the initial serum CPK activity in the 3 patients who expired showed an average value of 32.6±32.5 IU/L and when compared to survived group (25.76±19.0) the values were insignificant statistically ($p>0.05$). Initial serum CPK activity was within normal limits in 2 out of 3 expired patients, in the 3rd patient who expired on the 4th day of admission had serum CPK of 68 IU/L which fell to 18 IU/L on the 3rd day. The initial CPK activity in C.S.F. was significantly high in the expired group of patients (40.33±7.63 IU/L) compared to the survived group (15.3±8.5 IU/L). The interesting point was that the 2 patients who expired on the 4th day of admission demonstrated higher enzyme activity in C.S.F. on the 3rd day of admission as compared to the enzyme activity on the admission day.

The enzyme activity recorded in the C.S.F. in the 2 cases who expired on 4th day of admission was 47 IU/L and 42 IU/L on the admission day and 58 IU/L and 69 IU/L on the 3rd day of admission. The patient who expired on the 26th day of admission showed a gradual rise of CPK activity in C.S.F. from 25 IU/L on the admission day to 32 IU/L on the 14th day of admission in contrast to the linear drop of C.S.F. CPK in the survived patients. Thus it is obvious from the present study that a positive correlation exists between CPK activities in C.S.F. in cases of tubercular meningitis[10].

In the present study definite correlation was demonstrated between the enzyme activity in C.S.F. and level of consciousness, overall mortality, in cases of tubercular and pyogenic meningitis. The values of CPK were higher in unconscious and semi-conscious patients and still higher in patients who expired. We could not demonstrate any correlation of the enzyme activity either in serum or C.S.F. with the neurological deficit in both tubercular and pyogenic meningitis. It is obvious from the present study, that CPK estimation in C.S.F. in cases of pyogenic and tubercular meningitis may be an added tool in the diagnosis of these diseases, particularly in clinical situations where the other parameters to distinguish between the two types of meningitis are not well demarcated. Furthermore its estimation may also define the patients, who are at high risk regarding their ultimate prognosis.

Conclusion:

Creatine phosphokinase activity in cerebrospinal fluid (C.S.F.) has a diagnostic and prognostic value in patients of pyogenic and tubercular meningitis. There is no relationship between serum and cerebrospinal fluid (C.S.F.) creatine phosphokinase in patients of pyogenic and tubercular meningitis.

References:

1. Afshan Zeeshan Wasti, Farah Jabeen et al. Analysis of Cerebrospinal Fluid in Viral

Meningitis Patients. International Journal of Advanced Research. 2013; 1(8):69-74.
2. Kakuta E. [Creatine phosphokinase (CPK) activity in serum and cerebrospinal fluid in cerebrovascular disorders]. Rinsho Shinkeigaku.1973 Feb;13(2):102-10.
3. Richard F. Shaw, Carl M. Pearson, Sudhir R. Chowdhury et al. Serum Enzymes in Sex-Linked (Duchenne) Muscular Dystrophy. Arch Neurol.1967;16(2):115-122.
4. Anshu Gupta, Chhavi Gupta, Sarabjeet Khurana. Evaluation of total creatine kinase levels in a spectrum of neuro-psychiatric disorders in a tertiary neurosciences centre. International Journal of Medicine and Public Health. 2015;5(4):362-366.
5. Horder M, Elser RC, Gerhardt W et al. International Federation of Clinical Chemistry, Scientific Division Committee on Enzymes: approved recommendation on IFCC methods for the measurement of catalytic concentration of enzymes. Part 7. IFCC method for creatine kinase (ATP: creatine N-phosphotransferase, EC 2.7.3.2). Eur J Clin Chem Clin Biochem. 1991;29(7):435-56.
6. Bansal BC, Saini AS, Sood AK et al. Evaluation of creatine phosphokinase in cases of cerebrovascular accidents. J Assoc Physicians India. 1985;33(4):263-4.
7. Herschkowitz N Cumings JN. Creatine kinase in cerebrospinal fluid. J Neurol. Neurosurg. Psychiatry. 1964; 27: 247-250.
8. Roger M. Katz, William Liebman. Creatine Phosphokinase Activity in Central Nervous System Disorders and Infections. Am J Dis Child. 1970;120(6):543-546.
9. Roy A. E. Bakay, Arthur A. Ward. Enzymatic changes in serum and cerebrospinal fluid in neurological injury. Journal of Neurosurgery. 2012; 116(6):27-37.
10. Mehrotra TN, Mital HS, Goel VK et al. A study of CPK enzyme in cases of meningitis. J Assoc Physicians India. 1985;33(8):523-5.

Disclosure: No conflicts of interest, financial, or otherwise are declared by authors