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REVIEW ARTICLE

Ischemic Stroke and Serum CPK: A Review

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Introduction:

Stroke is characterized by the rapid appearance (usually over minutes) of a non-convulsive, non-traumatic focal deficit of brain function, most commonly a hemiplegia with or without signs of focal higher cerebral dysfunction (such as aphasia), hemi sensory loss, and visual field defect or brain-stem deficit. Provided that there is a clear history of a rapid-onset focal deficit, the chance of the brain lesion being anything other than vascular is 5% or less[1]. The neurovascular syndromes enable the physician to localize the lesion—sometimes so precisely that even the affected arterial branch can be specified[1,2] . Neuroimaging is very important to establish the diagnosis of ischemic stroke and further investigation are needed for evaluation of risk factors and to predict its prognosis.

As the stroke syndrome is usually clearly delineated clinically but in some patients, laboratory evidence of the presence of cerebral infarction may provide additional diagnostic and prognostic information. Determinations of serum enzyme activity have the advantage of permitting repeated sampling without danger or inconvenience to the patient. The variations in serum creatine kinase (CK) activity in patients presenting with acute ischemic stroke may correlate with the severity of disease.

CK is a dimeric globular protein consisting of two subunits with a molecular mass of 43 kDa. It buffers cellular ATP and ADP concentrations by catalyzing the reversible exchange of high-energy phosphate bonds between phosphocreatine and ADP produced during contraction. At least five isoforms of CK exist: three isoenzymes in cytoplasm (CK-MM, CK-MB and CK-BB) and two isoenzymes (non-sarcomeric and sarcomeric) in mitocondria[3].

CK-MM is found in several domains of the myofibre where ATP consumption is high and is a marker of muscle disease[4]. CK-MB increases in acute myocardial infarction [5]and CK-BB increases in brain damage [6]. Patients with neurological conditions such as acute cerebrovascular accidents[7], proximal spinal muscular atrophy[8] show marked elevation of CK-BB. Brain is a rich source of a variety of enzymes and any injury (e.g. stroke) to brain tissue could similarly result in an increase in activity of these enzymes in cerebrospinal fluid. A simultaneous increase in serum levels will probably depend on integrity of blood brain barrier. If injury is severe enough to disrupt the blood brain barrier there might be some rise in enzymatic activity in serum.

Pathophysiology of ischemic stroke:

Normal adult brain cerebral blood flow is 50 to 60 mL/100g/minute. Cerebral blood flow between 10 and 20 mL/100g/minute is considered consistent with ischemic penumbra. Cerebral blood flow below 10 mL/100g/minute is considered compatible with infarction. These delineations are not absolute because time is also a factor in the fate of tissue. Cerebral blood flows of 5 mL/100g/minute result in infarction within 30 minutes, whereas those between 5 and 15 mL/100g/minute result in infarction after 1 to 3 hours[9].So, occlusion of an intracranial vessel causes reduction in blood flow to the brain region it supplies. Ischemia produces necrosis by starving neurons of glucose and oxygen, which in turn results in failure of mitochondria to produce ATP. Without ATP, membrane ion pumps

stop functioning and neurons depolarize, allowing intracellular calcium to rise and elevation of lactic acid level with acidosis. . Cellular depolarization also

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causes glutamate release from synaptic terminals; excess extracellular glutamate produces neurotoxicity by activating postsynaptic glutamate receptors. The greatly increased concentration of glutamate (and aspartate) in extracellular space in a depleted energy state results in the opening of calcium channels associated with N-methy1-D-asapartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxanole propionate (AMPA) receptors. Persistent membrane depolarization causes influx of calcium, sodium, and chloride ions and efflux of potassium ions. Activation of the N-methyl-D-aspartate receptor by an increase in glutamate leads to a cascade of chemical reactions that ultimately leads to cell death ("theory of excitotoxicity"). Free radicals are produced by membrane lipid degradation and mitochondrial dysfunction. Free radicals cause catalytic destruction of membranes and likely damage other vital functions of cells. Lesser degrees of ischemia, as are seen within the ischemic penumbra, favor apoptotic cellular death causing cells to die days to weeks later.

Serum creatine kinase

The Enzyme creatine phosphokinase (CPK) is widely distributed in various organs, but especially high activities are present in skeletal muscle, heart, and brain[10]. Recent studies have shown that this enzyme exists in a number of different molecular forms or isozymes which can be demonstrated by various techniques such as agar gel electrophoresis. The isozyme pattern of brain consists of a single fast-moving fraction which differs from the slower moving fractions found in heart and skeletal muscle [11].

Mechanism of elevated serum creatine kinase

Serum enzymes are altered during the course of a number of diseases. The usual alteration is an increase in enzyme activity that can most frequently be attributed to destruction of tissue by ischemic necrosis or inflammation with liberation of soluble enzymes into the circulation. Decreased plasma clearance or increased productions of enzyme by a particular tissue are other contributing factors. In brain, CPK is considered to play an important role in cerebral metabolism by maintaining adenosine triphosphate concentrations[12,13].

Elevated Serum Creatine Kinase

Alterations in serum CPK activity has proved to be of diagnostic value in patients with muscular dystrophy and myocardial infarctions (Dreyfus et al., 1960). In these conditions the isozyme form found in the serum is the same as that of the tissue involved in the pathological process. Total serum CPK activity has been found to be elevated in patients following acute cerebrovascular accidents, with a gradual return to normal being observed.' Studies of CPK activity in the cerebrospinal fluid (CSF) have shown that elevations do occur following cerebral infarction or recurrent ischemia with residuum[14,15,16](Sherwin et al., 1967; Acheson et al., 1964; Nathan et al., 1967).

Relation of Ischemic Stroke With CK

Stroke is one of the leading causes of death in the world as well as the leading cause of acquired disability in adult in most regions [17,18]. Due to the tremendous burden that stroke places on our society, there have been major efforts to identify the severity according to serum creatine kinase (CK) and given treatment on those findings which could reduce the incidence of ischemic stroke (IS). The related study findings around the world have been sought in the followings-

AyH et al (2002) compared between creatine kinase-MB (CK-MB) and troponin T after stroke to determine whether troponin T increases in parallel to CK-MB[19]. They made daily measurements of CK-MB, myoglobin, total creatine kinase (total CK), and troponin T levels up to day 5 in 32 patients with large hemispheric infarction and with no history of coronary heart disease. The daily enzyme levels were compared with those of a control group of 22 patients with neurological diseases other than stroke. Serum CK-MB, myoglobin, and total CK levels were elevated above the cutoff value in 11, 26, and 20 patients with stroke, respectively. These enzyme levels gradually increased within the first 3 days and declined afterward. Troponin T did not exceed the reference range in any patients. One patient had elevated myoglobin and 3 had elevated total CK in the control group. The difference between groups was significant for CK-MB, myoglobin, and total CK at various time points. They concluded as Troponin T whether total CK and CK-MB elevations in stroke patients are likely to be noncardiac in origin.

Capocchi et al (1987) correlated with severity of brain damage in acute ischemic stroke patients with

serum CK-BB level[20]. They measured BB-CK activity in 11 patients with stroke and in 10 controls. Blood samples were taken 36 hours after the clinical stroke onset in every patient. Sera were stored at -80 degrees and analyzed within two months. The creatine kinase isoenzymatic pattern was determined by ion-exchange column separation and gradient elution system. The mean BB-CK concentration in patients with stroke was significantly higher than in controls (p less than 0.01). In the group of "stroke" patients they found a correlation between severity of brain damage, as suggested by the clinical picture and CT scans, and serum values of BB-CK.

Eisen & Sherwin (1968) tried to reveal serum creatine phosphokinase activity in cerebral infarction[21]. The results of serial serum creatine phosphokinase (CPK) activity observed in 20 patients each presenting with an acute neurological deficit are reported. Thirteen patients who were considered to have sustained hemispheric infarcts showed a rise in serum CPK activity. Four patients proved to have an underlying tumor or angioma. In these patients the serum CPK activity remained within normal limits during the course of their acute neurological deficit. It is suggested that the presence of high peak activities and an early rise in serum CPK may indicate a poor prognosis. Serum CPK activity is easily and fairly rapidly determined by the method used in the present study and may be a useful ancillary investigation in the diagnosis of a stroke syndrome.

Parakh et al (2002) estimated levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and creatine kinase (CK) in serum and cerebrospinal fluid of 25 patients of stroke, and were correlated with severity of disease[22]. 21 (84%) patients had ischemic stroke and four (16%) had hemorrhagic stroke. Serum and CSF AST levels were significantly elevated in the study group. The rise in CSF AST was more in the hemorrhagic subtype than in the ischemic subtype. Serum ALT and CSF LDH levels were also significantly elevated in patients with ischemic stroke. None of the enzyme levels were related to the severity of disease as assessed by the Glasgow coma scale.

Frederick et al (1984) conducted a study on acute ischemic stroke patients where Serum creatine kinase B (CKB) concentrations were measured in 38 patients during acute cerebrovascular diseases and in nine controls[23]. Mean CKB concentration was 6.2 ± 0.8 ng/mL. The fluctuation of the CKB concentration following ischemic stroke was as notable as the elevation immediately after the ischemic event. The two abnormalities were observed in 13 of 17 patients with acute cerebral infarction, and the extent of abnormalities roughly correlated with the volume of tissue damage.

Norris et al (1979) estimated serum cardiac enzyme levels (CK, LDH, SCOT) in ischemic stroke patients[24]. For that, they collected 288 patients (Group I) from a stroke intensive care unit and sixty-four of these patients, subsequently found not to have strokes, served as controls. Mean serum levels of all 3 cardiac enzymes were elevated in 8% of the 224 patients with stroke. The mean serum enzyme levels in patients with transient ischemic attacks (TIA) did not differ from controls. In a second group of 230 patients with stroke (Group II) serum CK levels were measured and the isoenzymes were fractionated to determine the tissue source of the enzymes. One hundred and one patients had raised total CK values and 25 of these (11%) had raised CK-MB (heart) iso-enzyme, the remainder having CKMM (skeletal muscle) fraction. No serum CK-BB (brain) iso-enzyme was detected in any patient. Patients with positive serum levels of CK-MB had more evidence of acute myocardial ischemia on ECG ($p < 0.05$), and more cardiac arrhythmias ($p < 0.001$) than those with normal CK levels. The acute rise in serum cardiac enzymes which they have recorded in the initial stages of stroke suggest that acute myocardial involvement is a commoner complication than is generally recognized. Also, since the CKMB rises were modest and progressive, it is more likely that this acute myocardial dysfunction is a consequence, rather than a cause, of the acute cerebrovascular lesion.

Myers et al (1982) examined on acute stroke patients to reveal resultant cardiac abnormalities including serum CK level[25]. Continuous 24 hour Holter ECG tapings were performed and serum

cardiac enzymes and plasma norepinephrine concentrations were measured within 48 hours after admission. Significantly, ($p < .001$) more serious arrhythmias were observed during 24 hour Holter ECG monitoring in stroke patients compared with controls and the difference remained ($p < .01$) after matching for age and co-existing heart disease. Arrhythmias were more common in older stroke ($p < .001$) and older control ($p = .05$) patients and with infarction of the cerebral hemispheres ($p < .05$) as compared to brainstem lesions. However, the 15 stroke patients with abnormally high CK values (mean 34.3 units) had a higher ($p < .02$) mean plasma norepinephrine concentration (650.4 pg/ml) than stroke patients with normal CK (427.7 pg/ml). They concluded as acute stroke may cause cardiac arrhythmias and myocardial cell damage.

Kloss et al (1985) found increase in the activity of creatine kinase BB isoenzyme (CK-BB) in the serum of patients with cerebrovascular disease[26]. The serum CK-BB activity of 33 patients with ischemic brain infarction, subarachnoid hemorrhage or intracerebral hemorrhage was measured with a bioluminescence method (CK-B Kit, LKB-Wallac) in combination with immunoprecipitation. The results were compared with lesions determined by computed tomography. In the control group (N = 19) there was a mean activity of 0.35 +/- 0.26 U/l (means +/- SE). In patients with small lesions (N = 11) the activity was 0.41 +/- 0.21 U/l, which was not significantly elevated when compared to the control group (Mann/Whitney U test). Therefore, patients with more extensive lesions (N = 12) and the group with severe lesions (N = 10) showed a significant elevation, with a mean activity of 0.61 +/- 0.34 U/l and 1.12 +/- 0.52 U/l, respectively. The group with severe lesions had a maximum activity on the first day after the initial symptoms.

Kaste & Somer (1978) detected heart type creatine kinase isoenzyme (CK MB) in the serum in 23 out of 53 patients (43%) with acute cerebrovascular, traumatic, or infectious brain damage[27]. Electrocardiogram disclosed abnormalities suggestive of acute myocardial injury in 15 of these 23 patients. Eleven of them also showed increased LD1 activity. Subendocardial haemorrhage was detected in 3 out of 8 necropsied patients with serum CK MB activity. Best of the 30 patients in whom no CK MB activity was found electrocardiographic abnormalities suggestive of acute myocardial injury were observed in 2 and increased LD1 was seen in 4 cases. The mortality was higher if either CK MB isoenzyme or electrocardiographic abnormalities suggestive of acute myocardial injury were present, compared with the patients lacking these signs (P less than 0.01). Present findings suggest that acute brain damage may secondarily cause myocardial damage more often than has been believed before. Results also indicate that a combination of acute brain damage and acute myocardial injury often indicated a poor prognosis.

In conclusion, patients with stroke have elevation of CKMB levels. And unlike CK-MB, troponin T does not increase after ischemic stroke. ECG changes are also observed in these patients. The elevation of CK-MB does not necessarily indicate acute coronary injury and ECG changes also do not correlate with myocardial damage in all cases.Therefore, elevated CK-MB levels do not translate into in vivo evidence of myocytolysis occurring after stroke. Especially important is the fact that CK-MB elevation in a stroke patient does not necessarily reflect an acute coronary event. Troponin T promises to be a valuable marker in this regard. Patients with stroke have to be carefully investigated for cardiac injury and CK MB levels elevation in these patients does not necessarily indicate any myocardial injury.

References:

1. Bradley WG, Daroff RB, Fenichel GM, Jankovic J, 2004, *Neurology in clinical practice. Principles of diagnosis and management,* 4th edn. Philadelphia: Butterworth-Heinemann
2. Aminoff MJ, 2001, Neurology and General medicine, 3rd edn, Philadelphia, Churchill Livingstone, pp. 1060-1067
3. Takagi Y, Yasuhara T, Gomi K, 2001, *Creatine kinase and its isozymes.* Rinsho Byori, 2001;116:52–61
4. Nigro G, Comi LI, Limongelli FM, Giugliano MAM, Politano L, Petretta V, Passamano L, Stefanelli S. Prospective study of X-linked progressive muscular dystrophy in Campania. Muscle Nerve. 1983;6:253–262
5. Borrayo SG, Sosa JF, Borja TB, Isordia SI, Arguero SR, 2006, *Qualitative determination of markers for myocardiac necrosis during pre-*

hospital admission for acute coronary syndrome. Cir, vol. 74, 231–35.

6. Pfeiffer FE, Homburger HA, Yanagihara T, *Creatine kinase BB isoenzyme in CSF in neurologic disease. Measurement by radioimmunoassay.* Arch Neurol, 1983; 40: 169–72
7. Bell RD, Rosenberg RN, Ting R, Mukherjee A, Stone MJ, Willerson JT, *Creatine kinase BB isoenzyme levels by radioimmunoassay in patients with neurological disease*. Ann Neurol, 1978; 3: 52–59.
8. Rudnik SS, Lutzenrath S, Borkowska J, Karwanska A, Hausmanowa-Petrusewicz I, Zerres K. *Analysis of creatine kinase activity in 504 patients with proximal spinal muscular atrophy types I–III from the point of view of progression and severity*. Eur Neurol,1998; 39: 154–162.
9. Marcoux FW, Morawetz RB, Crowell RM, DeGirolami U, Halsey JH., Jr Differential regional vulnerability in transient focal cerebral ischemia. Stroke. 1982;13:339–346
10. Colomb JP, Richterich R., and Rossi E.: Serum-Kreatin-Phosphokinase: Bestimmung und diagnostishe Bedeutung. Klin Wochenschr. 1962 Jan 1;40:37–44
11. Van Der Veen, K. J.. and Willebrand, A. F.: Isoenzymes of creatine phosphokinase in tissue extracts and in normal and pathological sera. Clin. chim. Acta 1966;13: (3)312-6
12. Mcilwain, H.: Cell-free cerebral systems: glycolysis and the pentose phosphate pathway. In: Biochemistry and the Central Nervous System. London: J. and A. Churchill Ltd., 1966; 83.
13. Pearce. J. M. S, Pennigton R. J, and Walton, J. N.: Serum enzyme studies in muscle disease. 11. Serum creatine kinase activity in muscular dystrophy and in other myopathic and neuropathic disorders. J. Neurol. Neurosurg. Psychiat. 1964;27:96
14. Sherwin, A. L., SIBER, G. R., and ELHILALI. M. M.: Fluorescence technique to demonstrate creatine phosphokinase isozymes. Clin. chim. Acta 1967; 17:245-249..'
15. Acheson, J., James D C, Hutchison E C and Westhead R.. Serum creatine-kinase levels in cerebral vascular disease. Lancet 1965; 285: 1306-07.
16. Nathan, M. J.: Creatine phosphokinase in the cerebrospinal fluid. J. Neurol. Neurosurg. Psychiat 1967: 30:52
17. Shi F, Hart RG, Sherman DG, Tegeler CH. Stroke in the People's Republic of China. Stroke. 1989;20: 1581–85.
18. Murray CJL, Lopez AD, eds., 1996, '*The Global Burden of Disease*.', Vol 1. Boston, Mass: Harvard University Press;113-16.
19. Ay H, Arsava EM, Saribas O. "Creatine Kinase-MB Elevation After Stroke Is Not Cardiac in Origin Comparison With Troponin T Levels", Stroke. 2002;33:286-89.
20. Capocchi G, Tassi C, Ricci S, Zampolini M, Fausti R, Rossi A.Creatine kinase BB activity in serum of patients with acute stroke: correlation with the severity of brain damage. Ital J Neurol Sci. 1987 ;8(6):567-70
21. Eisen AA, Sherwin AL. *Serum creatine phosphokinase activity in cerebral infarction, Neurology,* Minneap 1968;18:263-68.
22. Parakh N, H.L. Gupta, A. Jain, "Evaluation of Enzymes in Serum andCerebrospinal Fluid in Cases of Stroke" Neurology India 2002; 50: 518-19.
23. Frederick E. Pfeiffer, Henry A. Homburger, Takehiko Yanagihara, Serum creatine kinase B concentration in acute Cerebrovascular Diseases"*Arch Neurol.* 1984;41(11):1175-78.
24. Norris JW, Hachinski VC, Myers MG, Callow J, Wong T, Moore RW; Serum cardiac enzymes in stroke. Stroke. 1979:(10)548-53.
25. Myers GM, Noris WJ, Hachinski VC,Weinert ME, Sole MJ."Cardiac Sequelae of Acute Stroke", Stroke 1982; 13:838-42
26. Kloss R, Keller HE, Stober T, Emde H, Schimrigk K "Creatine kinase BB activity in the serum of patients with cerebrovascular diseases" Nervenarzt. 1985;56(8):417-22.
27. Kaste M, H Somer, A Konttinen "Heart type creatine kinase isoenzyme (CK MB) in acute cerebral disorders" *Br Heart J* 1978;40:802-805