Evaluation of CK MB levels in Acute Ischemic stroke

Dr. Bogarapu Kiranmayi M.D¹, Dr. V. Bhavani M.D², Dr. R. Tagore³
(Department of Biochemistry, Siddhartha Medical College, Vijayawada, Andhra Pradesh, India)

Abstract: Stroke is a cerebrovascular event in which neurological deficit develops over minutes or hours, sometimes in a stepwise fashion, persists for 24 hours or more and is caused by a vascular disturbance such as arterial occlusion with consequent ischemic focal infarction of the brain. Various studies in these patients with stroke have shown to have myocardial injury. Electrocardiographic (ECG) abnormalities also have been observed in these patients but most cases do not show acute coronary artery disease. Cardiac enzymes like creatine kinase myocardial sub fraction (CK-MB) which are specific for myocardial infarction loses its specificity in patients with stroke. CK-MB levels elevation in these patients does not necessarily indicate any myocardial injury. 50 patients with acute ischemic stroke of first occurrence and 50 age matched controls without cardiac or neurological disease were assessed for CK-MB levels. ECG changes were also recorded. There was significant elevation of CK-MB levels in 28% of the patients compared to the controls. ECG changes were observed in 32% of patients. CK-MB elevation in acute ischemic stroke is likely due to non cardiac reasons. ECG changes do not correlate with elevation of CK-MB suggesting the possibility of insufficient sensitivity of ECG in detecting acute myocardial injury. Abnormally high levels of plasma catecholamine secondary to rapidly increasing intracranial pressure, skeletal muscle injury caused by multiple injections, negative caloric balance may be some of the reasons attributed to the elevation of CK-MB levels in these patients. Autonomic neural stimulation from hypothalamus or elevated circulating catecholamines are the mechanisms for ECG changes found in patients with stroke.

Keywords: Cerebrovascular event, neurological deficit, ischemic focal infarction, myocardial injury, coronary artery disease, cardiac enzymes.

I. Introduction

Stroke is an acute or sub acute event in which a neurological deficit develops over minutes or hours, sometimes in a stepwise fashion, persists for at least 24 hours or more and is caused by a vascular disturbance in the brain. Most strokes are due to arterial occlusion and consequent ischemic focal infarction of the brain, primary intra cerebral hemorrhage being comparatively much less common. Several studies in stroke patients suggest myocardial involvement. Various electrocardiographic abnormalities have also been observed but not all cases show signs of ischemic myocardial injury. Myocardial injury after stroke or other acute cerebral lesions was attributed to abnormally high levels of plasma catecholamines secondary to rapidly increasing intracranial pressure.

The release of cardiac enzymes in the acute ischemic stroke was documented as early as the late 1970s. Cardiac enzymes like creatine kinase MB (CK-MB) are elevated in myocardial injury. CK-MB is an enzyme found mainly in the heart muscle, but also found in tongue, diaphragm, uterus, prostate and skeletal muscle, although in low amounts of only 1% to 3%. CK-MB that is specific of myocardial injury increases within 3-8 hours. It peaks at 9-24 hrs. and returns to normal by 48-72 hrs. Although CK-MB levels are elevated in myocardial damage, it may also be released as a result of damage to non cardiac muscle which decreases its specificity. Furthermore some patients may develop clinically important myocardial dysfunction due to sub lethal injury that does not result in CK-MB release. Many studies have shown increase in CK-MB levels and changes in electrocardiogram (ECG) after stroke (Norris et al. 1979; Rudehill et al, 1982; Brouwers et al, 1989; Kuroiwa et al, 1995). Every cerebrovascular accident is likely to exert considerable stress on the patients hearts. CK-MB activity has been shown to increase in certain patients with ischemic stroke, subarachnoid hemorrhage and head trauma in the absence of any clinically evident acute coronary syndrome. A continuing low grade myocardial necrosis suggestive of myocytolysis, the pathological hallmark of stroke-related cardiac damage distinguished by foci of swollen myocytes, interstitial bleeding, and mononuclear infiltration in the vicinity of cardiac nerves, has been implicated as the cause of CKMB elevations.

II. Aim Of The Study

The present study considers the evaluation of CK-MB in acute ischemic stroke. Evaluation of various parameters such as serum cholesterol, blood glucose are also done as the modifiable risk factors for ischemic stroke are hypertension and diabetes mainly followed by hyperlipidemia, smoking, excess alcohol consumption oral contraceptives and social deprivation. Changes in electrocardiogram have also been looked for.

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III. Materials And Methods

The present study was conducted on 50 patients admitted with acute ischemic stroke diagnosed as acute ischemic stroke. The study was conducted on patients admitted into Government General Hospital and Nagarjuna Hospitals, Vijayawada between January and April 2015. The diagnosis of acute ischemic stroke was confirmed by the neurologist, by way of history of focal neurological deficit lasting for more than 24 hrs. general examination, neurological examination and brain CT scan. 50 age matched individuals served as controls. They do not have evidence of either neurological or cardiac disease. History of risk factors like hypertension, diabetes mellitus, hypercholesterolemia, previous vascular event like myocardial infarction, stroke or peripheral embolism have been looked into, and patients selected accordingly.

Inclusion criteria:
1. Patients diagnosed with first ever acute ischemic stroke.
2. Age 40-70 years.

Exclusion criteria:
1. Ischemic heart disease
2. Heart failure
3. Major cardiac surgery
4. Chronic atrial fibrillation
5. Renal impairment
6. Hemorrhagic stroke and traumatic and space occupying lesions of cerebrovascular diseases were excluded by history and brain CT scan.

The blood samples were collected on the first day of onset of stroke. ECG changes were recorded at the time of admission. Random blood samples were collected into two clean bottles under aseptic conditions, one without anticoagulant and one with anticoagulant (sodium fluoride and potassium oxalate). Serum was separated taking precautions to avoid hemolysis. From the first bottle the following tests were done.

1. Estimation of Serum CK-MB by Immunoinhibition method. Principle: The serum is incubated with CK-MB reagent containing antibody specific to CK-M subunit which completely inhibits the CK-M monomer, leaving the activity of CK-B subunits unaffected. Thus, the CK-MB activity in the samples is calculated from the CK-B activity not inhibited, by the following reaction sequence.

\[
\text{CK-B} \\
\text{Creatine phosphate + ADP} \rightarrow \text{creatinine + ATP} \\
\text{Hexokinase} \\
\text{ATP + glucose} \rightarrow \text{glucose-6-phosphate + ADP} \\
\text{Dehydrogenase} \\
\text{Glucose-6-phosphate} \rightarrow \text{6-phosphogluconate + NADPH + H}^+ \\
\text{Prewarm at 37°C the required amount of the working solution. Pipette 1ml of working solution and 0.05ml of serum. Mix thoroughly and transfer the assay mixture immediately to the thermostated cuvette and start the stop watch simultaneously. Record the first reading at the 300th second and subsequently few more readings with 30 seconds interval at 340nm.} \\
\text{Calculations: Calculate the average change in absorbance per minute. Activity of CK-MB in IU/L = } \Delta \text{Absorbance / min x 6752} \\
\]

2. Estimation of Serum Total Cholesterol. Principle: The cholesterol esters are hydrolyzed into free cholesterol and fatty acids by cholesterol esterase. The cholesterol is oxidized by cholesterol oxidase to yield 4-cholesten 3-one and hydrogen peroxide as by product. Hydrogen peroxide together with 4-Aminoantipyrine and phenolic compound in the presence of peroxidase gives the colored quinonemine dye. The intensity of the color formed is proportional to the cholesterol concentration and can be measured photometrically between 480 and 520nm.

From the second bottle containing anticoagulant blood sample is processed for estimation of Blood Glucose.

1. Estimation of Blood Glucose by GOD-POD method. Principle: The substrate D-Glucose is oxidized by glucose oxidase to form gluconic acid and hydrogen peroxide. The hydrogen peroxide so generated oxidizes...
the chromogen system consisting of 4-amino antipyrine and phenolic compound to a red quinonemine dye. The intensity of the color produced is proportional to the glucose concentration and is measured at 505nm.

**Statistical analysis:** The results were analysed by student t test, and p value compared among the two groups.

### IV. Results

The present study comprises of 50 cases of acute ischemic stroke and 50 age matched controls between age group of 40-70 years. Cases included 28 (56%) males and 22 (44%) females whereas controls included 31(62%) males and 19 (38%) females. The mean age and S.D. of control and test group are 55±9.3 versus 58.6±7.7 years. 23 persons (46%) were positive for hypertension and 14 persons (28%) were positive for diabetes mellitus. ECG Changes were observed in 18 persons (36%).

The mean and S.D. of creatine kinase MB, serum total cholesterol and blood glucose (random sample) of the control group are within the established normal values.

**Table 1:** Various study parameter values mean, S.D., t & p values of Control and Test group

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean</th>
<th>S.D.</th>
<th>T value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK MB in controls</td>
<td>10.6</td>
<td>4.7</td>
<td>5.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>In cases</td>
<td>24.0</td>
<td>16.6</td>
<td></td>
<td>significant</td>
</tr>
<tr>
<td>S. T. Cholesterol in controls</td>
<td>176.0</td>
<td>20.4</td>
<td>3.99</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>In cases</td>
<td>204.0</td>
<td>43.4</td>
<td></td>
<td>significant</td>
</tr>
<tr>
<td>Blood glucose in controls</td>
<td>112.2</td>
<td>11.9</td>
<td>4.32</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>In cases</td>
<td>145.0</td>
<td>52.9</td>
<td></td>
<td>significant</td>
</tr>
</tbody>
</table>

**Diagram 1. Gender distribution of cases and controls**

**Statistical analysis:**

CK-MB levels are higher in patients of stroke than those obtained in controls (CK-MB 24.0±16.6 versus 10.6±4.7 [p value <0.0001]). It is significantly elevated.

Serum total cholesterol levels are significantly elevated in test group compared to controls (S.T.Cholesterol 204±43.4 versus 176.0±20.4 [p value <0.0001]). Random Blood Glucose levels are also significantly elevated in the test group compared to the control group (Bl. Glucose 145±52.9 versus 112.2±11.9 [p value <0.0001]).

### V. Discussion

The present study included 50 cases of acute ischemic stroke and 50 age matched controls, persons without neurological and cardiac diseases. As per the results obtained it is found that patients with acute ischemic stroke have significantly elevated levels of CK-MB compared to the control group (CK-MB 24.0±16.6 versus 10.6±4.7 [p value <0.0001]). CK-MB levels were elevated in 14 persons (28%).

**Comparative study:**

<table>
<thead>
<tr>
<th>Name of the study</th>
<th>% ↑ in CK-MB levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Markku Kaste,Hannu Somer, et al</td>
<td>22% ↑ in CK-MB</td>
</tr>
<tr>
<td>Ismail Apak, Kenan Iltumur, et al</td>
<td>45% ↑ in CK-MB</td>
</tr>
<tr>
<td>Hakan Ay, MD; Ethem Murat Arsava et al</td>
<td>34% ↑ in CK-MB</td>
</tr>
</tbody>
</table>

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The present study is consistent with the data of Markku Kaste, Hannu Somer, et al and that of Hakan Ay, et al. The possible mechanism of elevation of CK-MB could be:

- Increased intra cranial pressure or insular disinhibition leads to marked release of catecholamine by activation of central autonomic network after ischemic stroke, which can induce tachycardia, coronary vasospasm, coronary and peripheral vasoconstriction, and direct myocardial toxicity due to increased intracellular calcium\(^{12,18}\).
- In particular, involvement of the insular cortex is known to be associated with more frequent occurrence of cardiac complications after acute stroke, probably via an increased sympathetic tone mediated by the cerebral autonomic centres\(^{12,19}\).
- Patients with hemispheric infarctions are subject to skeletal muscle injury caused by multiple injections. Moreover, negative caloric balance may occur in some because of inappropriate oral or fluid restriction with concern for brain edema. The latter limits the amount of intravenous or nasogastric calories with liberation of calories from the skeletal muscle. Therefore, elevations in CK-MB might reflect a generalized lytic state, especially of the skeletal muscle\(^{8,10,20}\).

Serum total cholesterol levels are significantly elevated in patients with stroke compared to controls (S.T.Cholesterol 204±43.4 versus 176.0±20.4 \(p\) value <0.0001). Random Blood Glucose levels are also significantly elevated in patients with stroke compared to the control group (Bl. Glucose 145±52.9 versus 112.2±11.9 \(p\) value <0.0001). This statistical significance can be explained by the fact that coronary artery disease is highly prevalent among patients with diabetes and hypertension.

ECG changes were observed in 18 persons with stroke (36%), but it is not consistent with the increase of CK-MB.

### Comparative study:

<table>
<thead>
<tr>
<th>Name of the study</th>
<th>% of ECG changes</th>
</tr>
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<tbody>
<tr>
<td>Markku Kaste, Hannu Somer, et al</td>
<td>22% ECG changes</td>
</tr>
<tr>
<td>Ismail Apak, Kenan Ilhumur, et al</td>
<td>63% ECG changes</td>
</tr>
<tr>
<td>Ala Hussain Abbasse Haider, et al</td>
<td>45.7% ECG changes</td>
</tr>
<tr>
<td>Present study</td>
<td>36% ECG changes</td>
</tr>
</tbody>
</table>

The mechanisms that might mediate ECG changes in these patients are autonomic neural stimulation from the hypothalamus or elevated circulating catecholamines. Hypothalamic stimulation may cause ECG changes without associated myocardial damage whereas elevated catecholamines may result in myocardial damage. This might explain why so many patients have ECG changes and few have demonstrable myocardial damage in general, or ischemic damage in particular\(^{21}\).

The sample population that was analysed is small and analysis of a larger population is required for more accurate results.

### VI. Conclusion

Patients with stroke have elevation of CK-MB levels. 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. Stroke is highly prevalent among patients with diabetes and hypertension who may have preexisting coronary disease. Patients with stroke have to be carefully investigated for cardiac injury.

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