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"ISCHEMIA MODIFIED ALBUMIN: A BIOCHEMICAL MARKER OF ACUTE STROKE"

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ABSTRACT

Stroke is one of the leading causes of death and disability worldwide. Still there is no cost effective test available as a marker of this disease. Ischemia modified albumin (IMA) is a relatively new biomarker of ischemic events. It was recently demonstrated that IMA levels also increase in acute stroke. Therefore this study was undertaken to evaluate the role of IMA in acute stroke and to find out its correlation with oxidative stress. 33 hemorrhagic stroke patients and 35 thrombotic stroke patients were taken as cases and compared with 36 age and sex matched controls. Serum IMA and MDA along with other routine biochemical parameters were estimated both in cases and controls. The results were analyzed statistically. Serum IMA values were significantly increased both in hemorrhagic and thrombotic stroke cases in comparison to controls (p-value <0.0001). A significant positive correlation was found between serum IMA and MDA levels of stroke cases (r-value 0.88, p-value <0.0001). Thus we concluded that IMA generated during ischemia and reperfusion is also raised in acute stroke cases and can be used as a biomarker of acute stroke.

KEY WORDS: Stroke, Ischemia Modified Albumin, Malondialdehyde.

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INTRODUCTION

Stroke or cerebrovascular accident (CVA) is one of the leading causes of adult disability and the 2nd most common cause of death worldwide [1, 2]. The diagnosis of stroke is first made from clinical features and then imaging study is used to determine the type of stroke and to support the diagnosis [3]. Radiological imaging studies are often not useful during early stage of acute stroke and such facilities are not widely available, time consuming and very costly. Another approach for diagnosing acute stroke would be use of biochemical markers like ischemia modified albumin (IMA) [4, 5, 6]. IMA is a relatively new biochemical marker of ischemia. It is a metabolic variant of protein generated during acute ischemic conditions due to decrease in the binding capacity of albumin for transition metals, such as cobalt, nickel and copper [7, 8]. During ischemia and reperfusion, modification altering binding capacity of albumin to transition metals also occurs as a result of oxidative stress [9]. Taking into consideration of the above facts, the present study was conducted with an objective to evaluate ischemia modified albumin (IMA) in different types of cerebrovascular accidents and to find out its correlation with serum malondialdehyde (MDA), which is used as a marker of oxidative stress.

MATERIALS AND METHODS

This study was conducted in S.C.B. medical college, Cuttack. Stroke cases within 24 hours of presentation were considered as cases. Cases were diagnosed on the basis of clinical examination and the diagnosis was supported with MRI or CT. Those who were having any other type of ischemia, abnormal serum albumin, renal & cardiac insufficiency were excluded from study. Age and sex matched healthy persons were taken as controls. Blood samples were collected from all subjects. From cases blood samples were collected within 24 hours of onset of symptoms. Routine biochemical parameters like plasma sugar, serum urea, creatinine and albumin were estimated using Flexor-XL autoanalyser. Serum IMA was estimated using the method of Bar Or et al 2000 [10]. As IMA loses its ability to bind cobalt, known amount of cobalt was added to serum sample and unbound cobalt was measured as the intensity of color complex formed after reacting with dithiothreitol by spectrophotometer at 470 nm. IMA value was expressed in U/ml. One IMA unit is defined as “µgm of free cobalt in the reaction mixture per ml of serum sample”. Serum MDA was estimated by the method of Satoh et al[11]. Statistical analysis was done using SPSS 17 statistical package. The study has been approved by institutional ethical committee.

RESULTS

A total of 104 subjects were included in the study out of which 33 were acute hemorrhagic stroke, 35 acute thrombotic stroke and 36 age and sex matched healthy controls. In this study the mean age of hemorrhagic stroke was 58.24±12.35 years, thrombotic stroke was 60.29±11.54 years and of control was 54.81±11.20 years. Out of 33 hemorrhagic patients 19(57.6%) were male and 14(42.2%) were female, among 35 thrombotic stroke patients 18(51.4%) were male and 17(48.6%) were female and out of 36 controls 20 (55.6%) were male and 16(44.4%) were female. Routine biochemical parameters like fasting plasma glucose (FPG), serum urea, creatinine and albumin were as shown in table 1. The serum IMA and MDA values were described in table 2. There was a significant rise in serum IMA (p-value <0.0001) both in hemorrhagic stroke (98.19±17.52 U/ml) and thrombotic stroke (97.11±14.40 U/ml) in comparison to control (69.96±9.35 U/ml). Serum MDA documented a significant rise both in hemorrhagic stroke (3.34±0.59 nmol/ml) and thrombotic stroke (3.30±0.59 nmol/ml) when compared with control (1.60±0.41nmol/ml). The level of serum IMA of controls and acute stroke patients were depicted in Figure 1. The correlation graph (Figure 2) between serum IMA and MDA in study population also showed a significant positive correlation (r-value 0.88, p-value < 0.0001).

Table 1
Distribution of Demographic and Routine Biochemical parameters in controls and study groups

Parameters	Controls	Hemorrhagic Stroke	Thrombotic Stroke
Mean Age (Years)	54.81±11.20	58.24±12.35	60.29±11.54
Male:Female	20:16	19:14	18:17
FPG (mg/dl)	112.44±18.60	130.03±44.15	136.69±56.63
Serum Urea (mg/dl)	27.06±6.51	29.88±9.88	28.43±9.48
Serum Creatinine (mg/dl)	1.08±0.26	1.09±0.31	1.09±0.31
Serum Albumin (gm/dl)	4.31±0.44	4.17±0.65	4.06±0.45

Table 2
Distribution of Serum IMA and MDA in controls and study groups

Parameters	Controls	Hemorrhagic Stroke	Thrombotic Stroke
IMA (U/ml)	69.96±9.35	98.19±17.52**	97.11±14.40**
MDA (nmol/ml)	1.60±0.41	3.34±0.59**	3.30±0.59**

***** p-value <0.0001 in comparison to controls.***

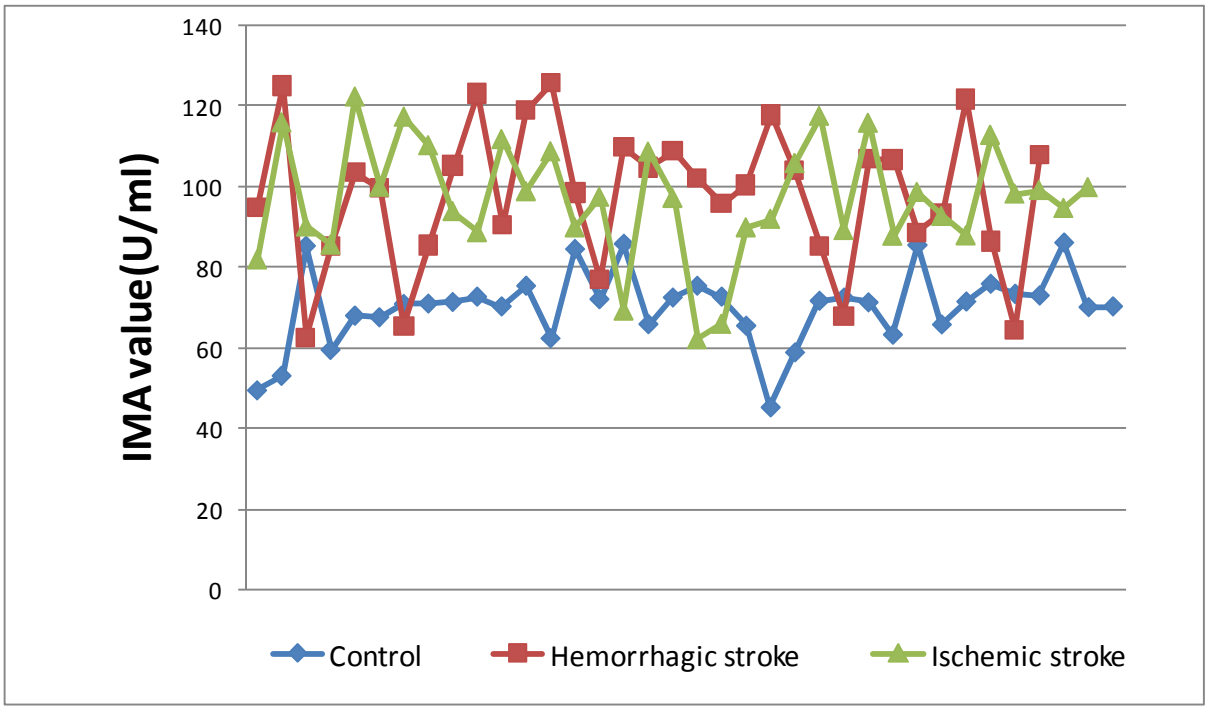

Figure 1
Scatter Diagram showing the IMA values in controls and study groups

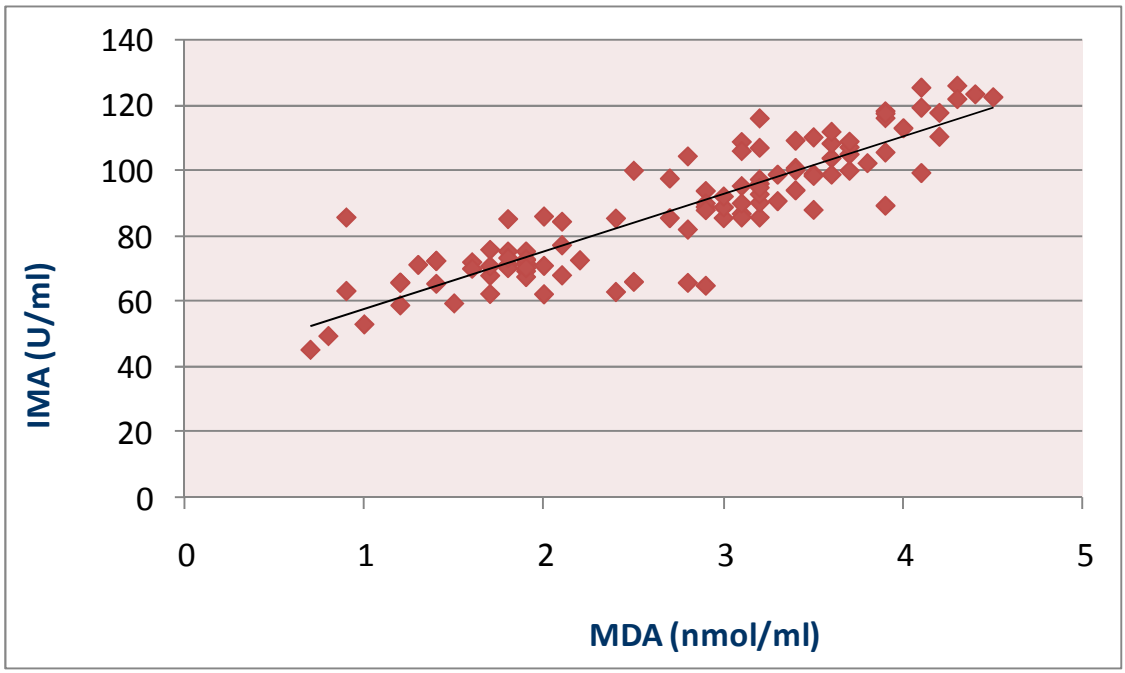

Figure 2
Correlation graph between serum IMA and MDA in study groups.
r-value 0.884, p-value <0.0001

DISCUSSION

IMA is a nonspecific marker of tissue ischemia, which has been previously mostly studied in patient with acute chest pain and shown to be increased in patients of myocardial ischemia either spontaneously or subsequent to percutaneous coronary intervention[12,13,14]. IMA is not specific for myocardial ischemia and can be increased after ischemia or injury in other organs [15,16,17,18]. In this present study we have estimated the IMA in acute stroke cases. This study registered a significant rise in serum IMA both in acute hemorrhagic and acute thrombotic stroke cases in comparison to controls. Findings of our study are consistent with Abboud et al[4] and Gunduz at al[5]. Abboud et al had recruited 118 patients in their study, out of which 84 were cases of brain infarct, 18 were brain hemorrhage and 16 were transient ischemic attacks. They found a higher value of IMA both in brain infarction and hemorrhage cases in comparison to other groups. Gunduz et al enrolled 106 patients, out of which 43 were brain infarction, 11 were brain hemorrhage, 52 were subarachnoid hemorrhage and 43 were controls. They were also found statistically significant differences in IMA value both in brain infarction and hemorrhage in comparison to controls. The N-terminal of albumin is an important site for binding heavy metals such as copper, nickel and cobalt. Modifications within the N-terminus end of albumin can occur either due to acetylation or deletion of amino acid leading to formation of IMA. Ischemic hypoxia that occurs in acute stroke leads to this modification of albumin forming IMA. In thrombotic stroke there occurs ischemia due to occlusion of intracranial vessels, where as in brain hemorrhage there occurs ischemia due to direct mechanical compression of brain tissue surrounding hematoma and to some extent due to extravasations of vasoconstrictors and pro-inflammatory substances. Edema developing following acute stroke further enhances the ischemic effect due to its mass effects. With increasing ischemia following acute stroke there occurs anaerobic metabolism of glucose leading to excess lactic acid production producing acidosis, which may also lead to IMA formation. Ischemia produces necrosis by starving neurons of glucose, which in turn leads to failure of mitochondria to produce ATP, which leads to impairment of energy dependant functions of cells including ion pumps. This energy dependant pump failure may also lead to generation of IMA [3,10,19]. This current study registered a significant rise in serum MDA level in acute stroke patients in comparison to controls. Our findings are similar to Beg et al [20] and Kossi et al [21], who observed increase in production of product of lipid peroxides in acute stroke. Our study also documented a significant positive correlation between serum IMA and MDA. This is in accordance with the work of Roy et al [9], Bahinipati et al[18], Behera et al[13] who suggested that increased IMA levels may result from increased oxidative stress. The brain being rich in lipids is particularly vulnerable to lipid peroxidation. During ischemia and reperfusion modification altering binding capacity of albumin for cobalt may occur as a result of acidosis, reduced oxygen tension and generation of free radicals, leading to formation of IMA.

CONCLUSION

The raised serum IMA level in acute stroke cases compared to control in the present study may be useful as a cost effective procedure in diagnosing the acute stroke, particularly where CT findings are not supportive in the emergency departments and the areas where these facilities are not available. However a wider series of study may be needed for better understanding and its clinical utility as a biomarker to discriminate stroke from other acute neurological conditions.

CONFLICTS OF INTEREST

We declared that we have no conflicts of interest.

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I dedicate this work to my beloved father late Pravash Chandra Jena.

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