Original article:**Assessment of serum Ischemia Modified Albumin (IMA) Levels in Acute Rheumatic Fever***Indranil Dawn¹, Gouranga Biswas²***Abstract:**

Introduction : Rheumatic fever (RF) is an autoimmune, multiorgan inflammatory disease. The patients develop carditis (50-78%), arthritis (35-88%), chorea (2-19%), erythema marginatum (< 6%) and subcutaneous nodules (< 1-13%). Ischemia modified albumin or cobalt binding albumin is one of new biomarker for inflammation and oxidative stress. Various previous studies indicate that acute rheumatic fever is associated with oxidative stress and inflammation. In the present study, we examined IMA, CRP, ESR and albumin levels in acute rheumatic fever. **Material and method:** This case control study was conducted between April 2017 to March 2018 in pediatrics department of Malda Medical College and Hospital. Study group composed of 42 children aged 5-18 years suffering from acute rheumatic fever diagnosed by modified Jones criteria and they compared with 50 healthy age and sex match control. The IMA levels were compared among groups, and the association to acute phase reactants were investigated. **Results:** Values of serum ischemia modified albumin, ESR and C Reactive Protein were significantly higher in cases compared to control group (p value ≤ 0.001). But no significant difference was found between values of serum albumin in cases compared to control group. Positive correlation was found between cases serum IMA and ESR, C-Reactive protein. **Conclusion:** Serum ischemia modified albumin were significantly higher in children with acute rheumatic fever compared to control group, so IMA could be used as a biomarker in diagnosis of ARF. However, further multicenter and larger case studies are needed to provide stronger evidence.

Keywords: Acute rheumatic fever, rheumatic heart disease, ischemia modified albumin.

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Introduction

Rheumatic fever (RF) is a childhood autoimmune and inflammatory disease. A β -hemolytic streptococcal infection is liable for acute RF in genetically susceptible individuals¹. The affected children may develop carditis (50-78%), arthritis (35-88%), chorea (2-19%), erythema marginatum (< 6%) and subcutaneous nodules (< 1-13%)² or some other complications. Heart related defect most dangerous result of acute RF. RF disease now a day diagnosed by modified 2015 Jones criteria³. Commonest complication of acute RF is chronic rheumatic heart condition⁴. Approximately 500 000 new RF cases and about 230 000 deaths occurs due to RF per annum globally⁵. Acute RF and chronic rheumatic heart condition (RHD)

remain a serious health problem in our country. Ischemia modified albumin or cobalt binding albumin is among the new biomarker for inflammation and/or oxidative stress. Ischemia modified albumin (IMA) is used to assay patient with ischemic incident like myocardial infarction, and many other acute and chronic condition. Many earlier clinical studies have demonstrated that IMA are often used for early diagnosis of acute myocardial infarct (AMI), IMA not only go with cardiac disease but also increase many other diseases like liver cirrhosis⁶, embolism,⁷ end stage renal disease⁸ and also cerebrovascular diseases.⁹⁻¹⁰

N-terminal region of human serum albumin is a binding site for transitional metal like cobalt, nickel and copper. Probably as

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a result of hypoxia, acidosis, free-radical injury, and energy-dependent membrane disruption, this binding site is altered and binding capacity with metal ion is reduced in presence of hypoxia or ischemia.¹¹ This structural modified albumin known as ischemia modified albumin (IMA). IMA is typically one percent to two percent of the entire serum albumin and increases to six to eight percent in patients with ischemia or any inflammatory condition. C-reactive protein (CRP) may be a type I acute phase response protein that's synthesized within the liver¹².

Various previous studies indicate acute RF is gone with oxidative stress and inflammation. Within the present study, we examined IMA, CRP, ESR and Albumin levels in acute RF.

Material and method

This case control study was conducted between April 2017 to March 2018 in the pediatric department of Malda Medical College and Hospital. Study group composed of 42 children aged 5-18 years suffering from acute rheumatic fever diagnosed by modified Jones criteria and they compared with 50 healthy age and sex match control. Exclusion criteria include other acute or chronic disease. The IMA levels were compared with cases and controls, and the association to acute phase reactants were investigated. The procedures followed were in accordance with the principles of the Declaration of Helsinki in 1964, as revised in 2013.

IMA measurement

Serum samples were collected from patients and controls. Samples were stored at -80°C until testing. 100 μL cobalt chloride was added on 35 μL of serum, and incubated for 5 minutes. 50 microliters of dithiothreitol (DTT) reagent was added to this mixture, and DTT forms a colored complex with cobalt¹³ which is not bound with albumin. Color complex was measured spectrophotometrically at 470 nm of wavelength. It was compared with a serum cobalt blank without DTT. Results were reported in absorbance units (ABSU).

Albumin measurement

Serum albumin was measured by bromocresol green method (BCG). BCG forms a colored complex with serum albumin. The intensity of the color, was measured at 620 nm of

wavelength, which was directly proportional to the concentration of Albumin.¹⁴

C-reactive protein

Nephelometric procedure was used to detect CRP. CRP in serum formed an antigen-antibody complex with the latex particles. Light scattering, measured by after 6 min, was proportional to the concentration of the CRP present in the sample.¹⁵

ESR estimation

ESR was measured by Westergren method.¹⁶

Statistical analysis

SPSS 19 computer program was used.

Results

Values of serum ischemia modified albumin, ESR and C Reactive Protein were significantly higher in cases compared to control group. In cases serum IMA were found 0.42 ± 0.05 while in the control group they were 0.34 ± 0.04 (p value ≤ 0.001). But no significant difference was found between values of serum albumin in cases compared to control group (Table 1, Figure 1).

Positive correlation was found between cases serum IMA and ESR, C-Reactive protein. (Table 2, Figure 3 and 4), but no significant relationship was found between serum IMA and serum albumin. (Table 2, Figure 2)

Figure 1: Value of serum ischemia modified albumin between case and control.

Figure 2: Correlation between serum ischemia modified albumin and serum albumin (case)

Figure 3: Correlation between serum ischemia modified albumin and ESR (case).

Figure 4: Correlation between serum ischemia modified albumin and C-reactive protein (case).

Table 1. Laboratory value between cases and controls.

	Mean $\pm$ SD (cases)	Mean $\pm$ SD (controls)	P value	T value
Serum IMA (ABSU/L)	0.42 $\pm$ 0.05	0.34 $\pm$ 0.04	≤ 0.001	7.2
Serum Albumin (gm/dl)	4.5 $\pm$ 0.4	4.6 $\pm$ 0.6	0.35	-0.93
ESR mm/hr	41.7 $\pm$ 7.1	11.9 $\pm$ 2.5	≤ 0.001	27.6
CRP (mg/L)	37.7 $\pm$ 10	9.8 $\pm$ 5	≤ 0.001	17.2

Table 2. Correlation between Ischemic modified albumin and other Laboratory value of cases.

Ischemic modified albumin, ABSU	Correlation coefficient	P value
Serum Albumin (gm/dl)	0.17	0.3
ESR mm/hr	0.75	≤ 0.001
CRP (mg/L)	0.52	≤ 0.001

Discussion

In our study we tried to investigate the role of ischemic modified albumin and other inflammatory marker in acute rheumatic fever. Serum ischemia modified albumin, ESR and C Reactive Protein were much higher in cases compared to regulate control group. But no significant difference was found between values

of serum albumin in cases compared to control group. ESR and C Reactive Protein also having positive correlation with serum IMA. IMA is produced due to the modification in structure of albumin as a result of the interaction between human serum albumin and heavy transition metals like cobalt, nickel and copper. Serum IMA changes thought to be associated with acute and/or chronic hypoxia or inflammation. IMA is additionally used to look at the alteration happening during the acute and chronic phases of myocardial ischemia¹⁷ or for other similar disorders.

Another study also showed IMA, ESR, and C-reactive protein serum levels of the acute RF group increased in comparison with the chronic rheumatic heart condition, different congenital heart valve disease, and control groups. The ischemia-modified albumin levels in both carditis and isolated arthritis subgroups of kids with acute RF were significantly high in comparison with control groups but in the chorea subgroup IMA level insignificant. Additionally, positive correlations were found between ischemia-modified albumin and different acute phase reactants (ESR and C-RP) of children with acute RF.¹⁸

Tokaret *et al.* and colleagues also observed that at the time of admission of acute RF suffering children, IMA levels were significantly increased ($p < 0.001$) compared with control and other groups. After treatment, statistically improvement was determined within the serum values of ESR (p ESR ($p < 0.001$), CRP ($p < 0.001$) and IMA ($p < 0.01$)¹⁹

But very few studies were conducted in Indian or subcontinent population. So, our study tries to prove relationship between IMA and other inflammatory markers like C reactive protein, ESR with acute rheumatic fever, so that it can be used as a novel diagnostic marker. We know that IMA associated with oxidative stress so antioxidant may be effective for treatment of acute rheumatic fever.

Conclusion

Serum ischemia modified albumin were significantly higher in children with acute rheumatic fever compared to control group. This

indicates that acute rheumatic fever is associated with inflammation. IMA could be used as a biomarker in diagnosis of ARF and however, further multicenter and larger case studies are needed to provide stronger evidence.

Conflict of interest: None declared.

Ethical approval issue: The study was approved

by the ethical comity Of Malda Medical College, Malda, West Bengal, India.

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Authors' contribution: Conception and design of the study:ID; Data collection and compilation: ID,GB; Data analysis:ID; Critical writing, revision and finalizing the manuscript: ID,GB.

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