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RESEARCH ARTICLE

Role of Serum S100A12 (Calgranulin C) as a Diagnostic and Follow-Up marker in Egyptian Children with Inflammatory Bowel Disease.

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Abstract: ***Background***: Inflammatory bowel disease (IBD) [ulcerative colitis (UC) and Crohn's disease (CD)] is a chronic, relapsing and remittent intestinal inflammatory disorder. Calgranulin-C (S100A12) is noninvasive marker of gut inflammation and has been previously reported elevated in various chronic inflammatory disorders such as rheumatoid arthritis, cystic fibrosis and more recently in IBD. Aim and Objective: The aim of this study is to evaluate the effectiveness of serum S100A12 in Egyptian children with inflammatory bowel disease (IBD) as a diagnostic and follow-up marker. Patients and methods: This study was carried on 60 children; classified into three groups: chronic disease group on remission (n=20); newly diagnosed group (n=20) and control group (n=20). The following were done for all patients: detailed history, complete general examination, local abdominal examination and examination of other systems and endoscopy findings. Serum S100A12 level Enzyme-linked Immunosorbent Assay Kit was used for quantification. Results: Our study found statistically noteworthy increased mean values of CRP and ESR in newly diagnosed group comparing to chronic disease group. Our study showed highly statistically noteworthy increased mean values of Serum S100A12 in Newly diagnosed group, followed by chronic disease group, and the lowest value in control group. There was a statistically significant positive correlation between fecal calprotectin with Serum S100A12 in Chronic disease cases group and newly diagnosed cases Groups. Conclusion: Serum s100A12 may be included in the diagnosis of IBD.

Keywords: Inflammatory bowel diseases; Ulcerative colitis; Crohn's disease; S100A12; Calgranulin C

INTRODUCTION

Episodic intestinal inflammation is a hallmark of the chronic, sometimes fatal inflammatory the inflammatory bowel disease (IBD) illness. Crohn's disease and ulcerative colitis are among them two primary forms of idiopathic intestinal disease that are distinguished by where and how deeply they affect the intestine wall. Both conditions have a genetic tendency, great morbidity, and neither is treatable. Lastly, both raise the chance of colon cancer.1

S100A12 belongs to the S100 protein family, which includes at least twenty-five low molecular weight (9-14 kDa) in humans. Because these proteins are 100% soluble in ammonium sulphate at normal pH, they go by the moniker S100. Moore made the initial identification of the S100 proteins in 1965. Later on, other members of this family have been located and described.

Genes within a narrow region of 1q21 encode the majority of these proteins.2 IBD has been examined in relation to S100A12.3 The efficacy of serum S100A12 as a diagnostic marker in inflammatory bowel disease patients was assessed by Hashem et al.4 They came to the conclusion that UC and CD can be detected noninvasively with serum S100A12.

The aim of this study is to evaluate the effectiveness of serum S100A12 in Egyptian children with inflammatory bowel disease (IBD) as a diagnostic and follow-up marker.

Patients and methods

Sixty (60) children from the Paediatric Department of the Faculty of Medicine at Al-Azhar University Hospitals (Al-Hussein and Sayed Galal Hospitals) participated in this case-control research, along with the Outpatient Clinic of Gastroenterology of the Paediatric Department.

Three groups were created out of the sixty kids that took part in this study: Group I consisted of twenty healthy children who served as a control group. Group II consisted of twenty children who were diagnosed with IBD and were in remission, as determined by the IBD index. Group III including twenty children newly diagnosed with IBD.
Inclusion criteria: Egyptian children. Age <18 years, children of both sexes, a confirmed endoscopic, radiographic, histological, and conventional clinic criteria.

Exclusion criteria: Patients with positive stool culture, medical history of significant gastrointestinal

surgeries, particularly those involving resection and anastomosis. Non-steroidal anti-inflammatory drugs and individuals suffering from conditions involving active inflammation.

MATERIAL AND METHODS

History taking including personal data and history. General examination including Vital indicators include blood pressure, pulse, temperature, and respiration rate and head, neck, upper limb and lower limb. Local abdominal examination including inspection, palpation, percussion and auscultation. Examination of other systems. Anthropometric measures, routine laboratory tests including acute phase reactants and total blood counts (ESR and CRP) and fecal calprotectin. Finally, endoscopy and biopsy surement of serum S100A12 were also done.

Enzyme-linked Immunosorbent S100 Calcium Binding Protein A12 Assay Kit (S100A12). USCN Life Science Inc. created Homo sapiens, or humans. For the purpose of quantitatively measuring S100A12 in human serum, plasma, tissue homogenates, cell culture supernates, and other biological fluids in vitro, a sandwich enzyme immunoassay kit has been developed.

In our investigation, the blood levels of S100A12 were assessed in relation to the levels of established inflammatory markers and the clinical features of the patients.

Statistical analysis:

The statistical software for social sciences, version 23.0 (SPSS Inc., Chicago, Illinois, USA), was used to analyze the recorded data. When the distribution of the quantitative data was parametric (normal), it was shown as mean± standard deviation and ranges; for non-parametric (non-normally distributed) variables, it was shown as median with inter-quartile range (IQR). Quantitative variables were also shown as percentages and numbers. Using the Shapiro-Wilk and Kolmogorov-Smirnov tests, data were examined for normality.

We conducted the following tests:

For comparing two means, the independent-samples t-test of significance was employed, and for comparing two groups in non-parametric data, the Mann Whitney U test was utilized. An analysis of variance (ANOVA) conducted in one direction when comparing more than two means.

Post Hoc test: When comparing several variables at once, Tukey's test was employed. When comparing groups using qualitative data, Fisher's exact test and the Chi-square test were used instead of the Chi-square test if the expected count in any cell was less than 5. If one or both of the sets of variables were skewed, the degree of relationship between them was evaluated using Spearman's rank correlation coefficient (rs).To determine the overall predictivity of the parameter and the optimal cut-off value with detection of sensitivity and specificity at this cut-off value, receiver operating characteristic (ROC) curve analysis was utilized.

Probability (P-value): A significant P-value was one that was less than 0.05. P-values less than 0.001 were regarded as extremely significant. P-value >0.05 was regarded as negligible

RESULTS

BLOOD investigation	**Chronic disease cases at follow up (n=20)**	**Newly diagnosed cases Groups (n=20)**	**Test value**	**P-value**
HB (g/dl) Mean±SD Range	 10.79±1.19 9.5-12.5	 9.84±0.63 8.9-11	3.167	0.003*
TLC (1000/mm3) Mean±SD Range	 11.86±3.20 8.4-18	 10.37±2.38 6.6-15	1.670	0.103
Eosinophil% Mean±SD Range	 1.30±0.41 1-2	 1.15±0.33 1-2	1.276	0.210
PLT (1000/mm3) Mean±SD Range	 469.00±149.05 200-617	 403.70±82.68 270-500	1.713	0.095
CRP mg/l Mean±SD Range	 6.20±2.53 3-10	 14.40±5.45 3-30	7.386	<0.001**
ESR mm/h Mean±SD Range	 10.0±3.97 5-15	 18.20±7.05 5-30	6.583	<0.001**

t-Independent Sample *t-test* for Mean±SD; Significant **(S):** at p-value <0.05; Highly Significant **(HS):** at p-value <0.001; Insignificant at p-value >0.05.

Table (1): Group comparison based on blood investigation.

Table 1 revealed that, a statistically significant difference in the mean Hb value between the group with chronic illness and the newly diagnosed group with a p-value of less than 0.05. Additionally, there was a statistically significant difference in the mean CRP and ESR values between the newly diagnosed and chronic illness groups with a p-value of less than 0.05. However, with a p-value of (p>0.05), there is no statistically significant difference between the groups in terms of HB (g/dl), TLC (1000/mm3), Eosinophil% and PLT (1000/mm3).

Stool investigations	**Chronic disease cases at follow up (n=20)**	**Newly diagnosed cases Groups (n=20)**	**Test value**	**P-value**
Blood (RBCs)				
No	6 (30.0%)	4 (20.0%)	0.533	FE0.465
Yes	14 (70.0%)	16 (80.0%)		
PUS				
No	8 (40.0%)	10 (50.0%)	0.404	FE0.525
Yes	12 (60.0%)	10 (50.0%)		
Mucus				
No	6 (30.0%)	8 (40.0%)	0.440	FE0.507
Yes	14 (70.0%)	12 (60.0%)		
Stool Culture				
No Growth	20 (100.0%)	20 (100.0%)	0.000	1.000
Fecal calprotectin (ug/g)				
Mean±SD	115.10±30.52	758.90±165.35	16.194	<0.001**
Range	80-187	471-1380		

x^2: Chi-square test for Number (%) & Fisher's exact test, when suitable **p-value>0.05** is insignificant;
t-Independent Sample t-test for Mean±SD

Table (2): Comparison of the groups based on stool investigations.

In table 2, a statistically significant increase in mean was observed. value of fecal calprotectin in newly diagnosed cases group comparing to chronic disease group, p-value (p<0.001) in mind, while there is no statistically notable variations between the groupings in accordance with to stool investigations about Blood, PUS, Mucus, Stool Culture, p-value (p>0.05) in place.

Colonscopy finding	**Chronic disease cases at follow up (n=20)**	**Newly diagnosed cases Groups (n=20)**	**Test value**	**P-value**
Pancolitis	8 (40.0%)	6 (30.0%)	0.429	0.513
Distal colitis	6 (30.0%)	4 (20.0%)	0.520	0.471
Patchy colitis	6 (30.0%)	6 (30.0%)	0.000	1.000
Ulcer	6 (30.0%)	10 (50.0%)	1.625	0.202
Ilieitis	6 (30.0%)	6 (30.0%)	0.000	1.000
Rectosigmoidal colitis	0 (0.0%)	4 (20.0%)	4.333	0.037*

x^2: Fisher's exact test where suitable, p-value>0.05 is not significant, and Chi-square test for Number (%)

Table (3): Comparison between groups according to colonscopy finding.

Table 3 shows, statistically significant higher frequency of Rectosigmoidal colitis was 4 patients (20%) in newly diagnosed group, while there is no cases of Rectosigmoidal colitis in chronic disease group, p-value (p=0.037) in place.

	Chronic disease cases at follow up (n=20)	**Newly diagnosed cases Groups (n=20)**	**Test value**	**P-value**
Upper Endoscopy Finding				
Duodenitis	4 (20.0%)	6 (30.0%)	0.222	0.638
Esophagitus	4 (20.0%)	0 (0.0%)	4.032	0.045*
Gastritis	4 (20.0%)	14 (70.0%)	4.569	0.033*
Hiatus Hernia	2 (10.0%)	2 (10.0%)	0.000	1.000
Pan	0 (0.0%)	2 (10.0%)	0.625	0.429

Biopsy Result				
Duodenitis	2 (10.0%)	8 (40.0%)	1.804	0.179
H Pylori Gastritis	2 (10.0%)	6 (30.0%)	0.937	0.333
Non Specific Gastritis	2 (10.0%)	8 (40.0%)	1.804	0.179

x^2: Fisher's exact test and Chi-square test for Number (%), when applicable; **p-value >0.05** indicates insignificance, **p-value <0.05:** indicates significance, and **p-value <0.001:** indicates highly significant.

Table (4): Comparison between groups according to upper endoscopy finding and biopsy result.

Table 4 showed that, the chronic group had a statistically significant greater frequency of esophagitis than the newly diagnosed group, with a p-value of less than 0.05. With a p-value of less than 0.05, the newly diagnosed group had a statistically significant greater frequency of gastritis than the chronic group; however, there was no statistically significant difference between the groups based on the biopsy results (p>0.05).

Serum S100A12	**Chronic disease cases at follow up (n=20)**	**Newly diagnosed cases Groups (n=20)**	**Control Group (n=20)**	**Test value**	**P-value**
Mean±SD	148.22±24.41B	335.26±108.68A	103.17±37.45C	65.804	<0.001**
Range	109.7-210.5	180.1-527.1	63.7-195		
Tukey's test					
GI vs. GII		**GI vs. GIII**		**GII vs. GIII**	
<0.001**		0.040*		<0.001**	

In a single way, an analysis of variance test was run for Mean±SD, and a ***post-hoc test*** was used to compare groups many times. The Tukey test. Various capital letters denote a significant difference between the means in the same row at (p<0.05); ****p-value <0.001** is extremely significant.

Table (5): Comparison of the groups based on serum S100A12.

Table 5 shows, highly statistically noteworthy increased average value of Serum S100A12 in Newly diagnosed group was 335.26±108.68, followed by chronic disease group was 148.22±24.41B, and the control group's lowest value was 103.17±37.45, p-value (p<0.001) in place.

Fecal calprotectin (ug/g)	**Serum S100A12**	
	Rs	**p-value**
Chronic disease cases group	0.852	<0.001**
Newly diagnosed cases Groups	0.745	<0.001**

p-value>0.05 **(NS)**; *p-value <0.05 S; **p-value <0.001(HS)

Table (6): Correlation between fecal calprotectin (ug/g) and Serum S100A12 among study group, using Pearson Correlation coefficient **(rs).**

A statistically significant positive connection was found in table 6 between fecal calprotectin (ug/g) with Serum S100A12 in Chronic disease cases group and Newly diagnosed cases Groups, with r-value (r= 0.852 and 0.745) respectively, and p<0.001).

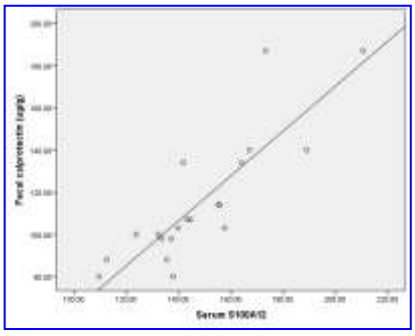

Figure (1): Correlation between fecal calprotectin (ug/g) and serum S100A12 in chronic disease group.

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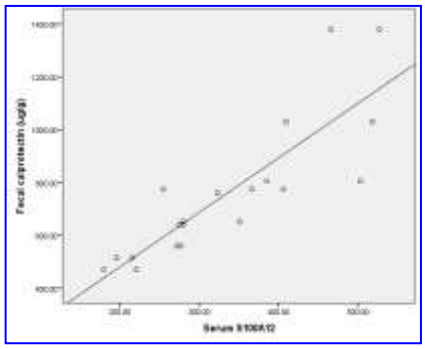

Figure (2): Correlation between fecal calprotectin (ug/g) and serum S100A12 in newly diagnosed group.

DISCUSSION

The term "inflammatory bowel disease" (IBD) describes a group of inflammatory digestive tract illnesses that have a chronic, relapsing-remitting course. There are two primary types of IBD: ulcerative colitis (UC) and Crohn's disease (CD). Clinical symptoms, patient-reported outcomes, and inflammatory load are the main factors used to categorise individuals and determine the severity of the illness in UC and CD. These indicators are often created in a research context. One major challenge for researchers developing predictive biomarkers for IBD is the absence of consensus on valid, trustworthy and significant outcome measures.5

Calgranulin C, or S100A12, is a calcium-binding protein having pro-inflammatory characteristics. It has been shown to be a marker for inflammatory bowel illness and is substantially expressed in a number of inflammatory disorders. It's possible that S100A12 has the greatest capacity to initiate RAGE. A proinflammatory response has been shown to occur when S100A12 binds to RAGE, both in vivo and in vitro. This response involves increased production of interleukin (IL)-6, IL-1, and tumor necrosis factor as well as the activation of nuclear factor kB. Reducing inflammation and atherosclerosis was achieved by blocking RAGE using anti-RAGE IgG or soluble RAGE, a decoy version of the receptor that restricts ligand access to RAGE.6

In our study, the mean age for patients with chronic disease was 6.40±2.97 years, while the mean age of newly diagnosed patients was 8.98±3.47 years and the mean age of control group was 7.40±2.10 years. There is statistically non-significant difference between the studied groups regarding age. Also, in the study of Lucaciu et al.7 between healthy individuals and CD or UC patients, there were no statistically significant changes based on age or gender.

We found that inflammatory bowel diseases occur more frequently in men, with statistically insignificant gender difference between the groups under study.

According to Esmat et al.8 the male:female ratio was 1:1.15, indicating a marginal rise in the prevalence of afflicted females in comparison to other regions of the world.

The study found that, the newly diagnosed case group had a statistically significant higher mean value of fecal calprotectin ($p < 0.001$) than the chronic disease group. However, there was no statistically significant difference between the groups based on stool investigations including blood, pus, mucus and stool culture ($p > 0.05$).

Furthermore assessed by Akutko et al.9 was the value of fecal calprotectin in the differential diagnosis of non-inflammatory gastrointestinal tract illnesses in children and CD. They discovered that children with Crohn's disease had considerably greater levels of fecal calprotectin than did controls ($p < 0.001$). Faecal calprotectin, they concluded, is helpful in monitoring the clinical course of Crohn's disease and in differentiating it from non-inflammatory gastrointestinal tract disorders in children; but, it is not beneficial in assessing the disease's activity and phenotype.

The newly diagnosed group had a statistically significant higher mean CRP value than the chronic illness group, according to our study, with a p-value of less than 0.05. Furthermore, C-reactive protein was shown to be considerably greater in children with Crohn's disease compared to controls ($p < 0.001$) by Akutko et al.9 They came to the conclusion that while C-reactive protein, erythrocyte sedimentation rate, and seromucoid are helpful in distinguishing Crohn's disease in children from other non-inflammatory gastrointestinal tract conditions and in tracking the disease's clinical progression, they are not useful in assessing the disease's activity or phenotype.

Our research revealed that the newly diagnosed group had a statistically significant higher mean ESR value than the chronic illness group, with a p-value of less than 0.05.Additionally, Akutko et al.9 discovered that children with Crohn's disease had erythrocyte sedimentation rates that were considerably greater than those of controls ($p < 0.001$).

Regarding S100A12, our study showed highly statistically significant higher mean value of Serum S100A12 in Newly diagnosed group was 335.26±108.68, followed by chronic disease group was

148.22±24.41B, and the lowest value in control group was 103.17±37.45, with p-value (p<0.001).

Hashem et al.4 evaluated the use of serum S100A12 as a diagnostic marker in individuals suffering from inflammatory bowel disease and irritable bowel syndrome. They showed highly significant elevation of serum S100A12 levels in UC patients (groups III and IV) in comparison with IBS patients (group II) and control group (group I), but no significance shown between IBS patients (group II) and control group (group I). Also, they showed a significant elevation of serum S100A12 levels in patients with high activity in clinical activity index (CAI) and colonoscopic activity index in comparison with lower stages of disease activity by CAI and lower colonoscopic activity index.

Carvalho et al.10 indicated that the most effective clinical use of S100A12 is in the distinction between IBD and IBS, with measures of serum S100A12 being performed by faecal S100A12.

A statistically significant positive association was found in our study between fecal calprotectin (ug/g) with Serum S100A12 in Chronic disease cases group and Newly diagnosed cases Groups, with r-value (r= 0.852 and 0.745) respectively, and p<0.001).

Hashem et al.4 showed serum S100A12 levels correlate significantly with other inflammatory parameters in UC patients (ESR and CRP).

CONCLUSION

Our results support the notion that S100A12 overexpression is not limited to the walls of an intestine inhabited by IBD, but rather is mirrored systemically and subsequently found in serum. Serum S100A12 levels are elevated in IBD patients and have a strong correlation with CRP, a "classic" measure of inflammation. However, serum S100A12 has a little diagnostic usefulness when used alone; hence, combining it with a "palette" of other serological markers may actually increase overall diagnostic performance. As a result, serum s100A12 may be used to diagnose IBD.

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