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Evaluation of adult immunoglobulin A vasculitis with oxidative stress and inflammation biomarkers

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Abstract

IgA vasculitis (IgAV) is a leukocytoclastic vasculitis affecting small vessels and is more common in children than in adults. In this study, we aimed to investigate the effects of oxidative stress in adult IgAV patients by Dynamic Thiol Disulfide Homeostasis (DTDH) and Ischemia Modified Albumin (IMA) levels. We also aimed to correlate the presence of inflammation detected by C-Reactive Protein (CRP) and Highly Sensitive C-Reactive Protein (hsCRP) with these oxidative stress parameters. Forty-one IgAV patients and forty-five controls were included in the study. Patients were classified as "active" or "in remission" according to the British Vasculitis Activity Score (BVAS). Measured parameters were compared between the groups. DTDH, IMA, CRP and hsCRP parameters were analyzed in both patient and control groups. According to our results, disulfide ($p=0.047$), index 1 ($p<0.001$), index 2 ($p<0.001$), IMA ($p<0.001$), CRP ($p=0.005$) and hsCRP ($p=0.004$) levels were significantly increased while native thiol ($p<0.001$), total thiol ($p<0.001$) and index 3 ($p<0.001$) levels were significantly decreased in IgAV patients. The results of this study show that oxidative stress is associated with IgAV disease and also with disease severity. The oxidative stress parameters evaluated were also correlated with markers of inflammation.

Key words: Immunoglobulin A vasculitis, dynamic thiol disulphide homeostasis, IMA, CRP, hsCRP

Introduction

IgA vasculitis (IgAV, formerly known as Henoch-Schönlein purpura (HSP)) is a leukocytoclastic vasculitis of small vessels. Polymorphonuclear leukocyte (PMNL) infiltration in vessel walls and IgA, C3 and immune complex accumulation is typical of organ biopsies in this disease [1]. IgAV is more frequent in children however no serious organ damage is seen in that age. Although the incidence is quite low in the adult population around 1/1.000.000, inclusion of joints, gastrointestinal and renal systems are more common when compared to pediatric population besides dermatological symptoms [2]. This low incidence limits the number of studies carried on in adult IgA patients.

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Human life depends on oxygen and aerobic processes and reactive oxygen species (ROS) are the harmful byproducts of human metabolism. The oxidative effects of ROS are neutralized by the antioxidant capacity of cells during normal cellular homeostasis. Increased production of ROS under stress conditions may cause various health problems [3]. Organic compounds with sulphydryl groups contain sulphur and hydrogen atoms and are referred as thiols (-SH). Thiols are very sensitivite to oxidation. Disulphides (SS), are the foremost critical course of covalent bonds shaped between two thiol bunches, they are energetic bonds and they are moreover redox touchy. The SH groups in thiols act as substrates for antioxidant enzymes and free radical scavengers. Under oxidative stress, these SH groups transform into reversible SS bonds. These bonds can be reduced back to the thiol group and the so-called “dynamic thiol disulphide homeostasis” is maintained (DTDH). The increase in SS and decrease in native thiols (SH) is accepted as a proof of oxidative stress exposure [4].

N-terminal region of the major plasma protein albumin can bind heavy metals like nickel, copper and cobalt. Hydroxylated free radicals can damage this N-terminal region so albumin can not bind these heavy metals properly. This altered form of albumin is called ischemia modified albumin (IMA) [5]. The detection of IMA levels can give valuable information about exposure of albumin to ROS.

C-reactive protein (CRP) discharged from hepatocytes is an acute phase protein. It is often associated with a lot of pain. High-sensitivity C-reactive protein (hsCRP) is more sensitive than standard CRP and can more effectively measure inflammation [6].

To our knowledge, oxidative stress and inflammation markers have not been evaluated together in a very rare disease such as adult IgAV. Our study evaluates oxidative stress in adult IgAV together with DTDH and IMA levels. It also evaluates these parameters together with the commonly used acute phase reactant CRP and its more sensitive form, hsCRP. Therefore, this is the first study to investigate disease pathogenesis and severity in adult IgAV disease with this test combination (DTDH, IMA, CRP hsCRP). The aim of this study was to evaluate DTDH and IMA levels together with CRP and hsCRP levels in adult IgAV patients and to investigate their relationship with inflammation, which is considered to be part of the disease pathogenesis.

Material and Methods

Study population

41 patients with IgAV and 45 healthy volunteers were included in this study according to the criteria of the American College of Rheumatology (ACR) [7]. The ACR criteria classified patients with IgAV according to (1) palpable purpura; (2) age of onset ≤20; (3) inflammation and (4) vessel wall granulocytes in arteriole and venule biopsy. A patient is diagnosed with IgAV when at least 2 out of 4 samples have been processed. Demographic characteristics of all participants were recorded. Age <18 or >65, any acute or chronic disease, hematological disease, malignancy, pregnancy and breastfeeding were the exclusion criteria for our study.

This research was affirmed by the local Institutional Review Board (approval number: E2-21-403) and composed educated assent was gotten from all members in understanding with the Declaration of Helsinki.

Clinical examination

Purpura, arthralgia, and abdominal pain have been described as the "classic triad" of IgAV. Skin biopsy shows leukocytoclastic vasculitis (LCV) or IgA vasculitis. Disease activity was classified as 'active' or 'in remission' according to the Birmingham Vasculitis Activity Scale (BVAS) criteria [8]. BVAS ≥1 was considered "active". The severity of the disease is measured by the involvement of different diseases/systems and increases with the score. Disease activity was determined by worsening of symptoms at the time of examination or within the last 28 days [9].

Sample collection and measurement of parameters

Participants received venous blood after fasting for 12 hours. BD Eclipse blood collection needle and BD Vacutainer blood tubes were used during blood collection. Patients' sera were used for the study. Centrifuge the sample at 3500 x g for 10 minutes. Separate the liquid into eppendorf tubes and store at -80°C until analysis. IMA levels [10] (The upper limit of linearity for IMA was 3.500 ABSU. Minimum CV%: 3.1) and DTDH parameters [11] (The upper limit of linearity for native thiol and total thiol was 4000 μM and 2000 μM for disulfide. Minimum CV% for all parameters: 2.9) were examined spectrophotometrically (Analyzes were performed with Roche Cobas 501 Clinical Chemistry Analyzer.). CRP (linearity: 5-300 mg/L, minimum CV%: 2.4) and hsCRP (linearity: 0.2-80 mg/L, minimum CV%: 2.7) levels were measured by immunonephelometry and all results were recorded (Analyzes were performed with Beckman AU680 Clinical Chemistry Analyzer.). Calculate the DTDH index and save all data. (Index 1: SS/SH*100, Index 2: SS/(SS+SH)*100, Index 3: SH/(SS+SH)*100).

Statistical analysis

IBM SPSS Statistic v.22 programme was used for statistical analyses. Shapiro-Wilk test was applied for normality testing. Student t test and Mann Whitney-U test were used for the analysis of numerical values while Chi-square test was used for the analysis of nominal variables. Pearson and Spearman tests were used for correlation analysis. $p<0.05$ was accepted

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statistically significant for all variables. ROC analysis was carried out to detect sensitivity and specificity of tests. Binary logistic regression analysis was performed to determine the parameter combination that performed best in differentiating the patient and control groups.

Results

There were 41 patients (14 women, 27 men) in the IgAV group and 45 patients (16 women, 29 men) in the control group. Age distribution was similar between the groups (45.73±17.53 vs. 42.16±13.79). Table 1 shows the characteristics of the patients. The course of was 46.35±6.79 months.

The most common symptoms were palpable purpura (100%), arthritis (56.1%) and/or neck pain (61%) and abdominal pain (46.3%). Eighteen (43.9%) of 41 patients had a BVAS score of ≥1 and were working, and 23 (56.1%) were not working. In skin biopsies, LCV was detected in 28 (68.3%) patients and 11 (26.3%) patients. Renal biopsy was performed in two patients showing IgA deposition in the glomeruli. The most common treatment strategies are steroids and steroid combined immunosuppressants, with a mean treatment duration of 8 months (5-16). The mean and median glucocorticoid (GC) dose was 3.9 g (0-18 g) and 7, respectively.

5 months (0-72 months), respectively. SH, SS+SH, and Index 3 were lower in the patient group, while SS was higher in Index 1, Index 2, IMA, CRP, and hsCRP inactive, Index 1, and Index 2 (Table 2).

CRP and hsCRP correlated positively with Index 1, Index 2, and IMA, and negatively with SH, SS+SH, and Index 3 (Table 3). ROC (receiver operating characteristic) analysis was performed to determine the absence of peak value (shape) (Figure 1). The results are shown in Table 4.

Binary logistic regression analysis showed that a combination of measured native thiol, IMA and hsCRP could correctly classify 97.6% of cases (Table 5).

Table 1. The characteristics of patients with immunoglobulin A vasculitis

Feature	All patients (N=41)
Age, y, mean (SD)	45.73±17.53
Disease duration, mo, mean (SD)	40.90±6.79
Gender	n (%)
Female	14 (34.15)
Male	27 (65.85)
Disease activity (Birmingham Vasculitis Activity Score)	n (%)
Active	18 (43.9)
Inactive	23 (56.1)
Skin involvement	40 (97.6)
Renal involvement	22 (53.7)
Gastrointestinal involvement	16 (39)
Vascular involvement	2 (4.9)
Arthritis	23 (56.1)
Arthralgia	25 (61)
Hypertension	2 (4.9)
Extremity edema	1 (2.4)
Abdominal pain	19 (46.3)
Weight loss	3 (7.3)
Myalgia or muscle weakness	10 (24.4)
Purpura	41 (100)
Proteinuria	13 (31.7)
Hematuria	7 (17.1)
Presence of biopsy	39 (95.1)
Site of biopsy	n (%)
Skin	33 (80.5)
Renal	2 (4.9)
Skin+renal	6 (14.6)
Pathological diagnosis	n (%)
Immunoglobulin A vasculitis	13 (31.7)
Leukocytoclastic vasculitis	28 (68.3)
Treatment	n (%)
Steroid	20 (48.8)
Steroid+immunosuppressant	18 (43.9)
Nonsteroidal anti-inflammatory drugs	1 (2.4)
No treatment	2 (4.9)
Treatment duration, median (interquartile range)	8 (5-16)

Table 2. Intergroup distribution of serum SH, SS+SH, SS, Index 1, Index 2, Index 3, IMA, CRP and hsCRP

Parameters	IgAV patients (n=41)	Controls (n=45)	p	Active disease	Inactive disease	p
SH (µmol/L)	301.6 (90.34)	404.3 (43.85)	<0.001*	232.59 (66.20)	355.62 (67.12)	<0.001*
SS+SH (µmol/L)	336.7 (95.71)	435.6 (43.96)	<0.001*	266.09 (72.78)	391.89 (72.80)	<0.001*
SS (µmol/L)	16.75 (12.70-29.10)	16.25 (8.05-17.70)	0.047*	15.60 (13.05-29.10)	17.75 (12.70-27.60)	0.124
Index 1	6.13 (1.47)	3.91 (0.69)	<0.001*	7.39 (1.25)	5.14 (0.63)	<0.001*
Index 2	5.43 (1.14)	3.62 (0.60)	<0.001*	6.42 (0.94)	4.65 (0.52)	<0.001*
Index 3	89.14 (2.30)	92.76 (1.21)	<0.001*	87.16 (1.88)	90.69 (1.05)	<0.001*
IMA (ABSU)	0.866 (0.08)	0.640 (0.06)	<0.001*	0.886 (0.08)	0.850 (0.08)	0.147
CRP (mg/L)	9.50 (0.30-112.50)	2.30 (0.30-21.20)	0.005*	10.0 (0.30-56.50)	9.50 (0.80-112.50)	0.724
hsCRP (mg/L)	8.10 (0.20-93.50)	1.90 (0.10-21.50)	0.004*	7.95 (0.20-42.30)	8.40 (0.60-93.50)	0.759

p <0.05 was considered statistically significant. * p-values represent differences between parameters

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Table 3. Correlation relationship of parameters

		Native thiol	Total thiol	Index 1	Index 2	Index 3	IMA
CRP	r	-0.459	-0.455	0.386	0.387	-0.387	0.236
	p	<0.001	<0.001	<0.001	<0.001	<0.001	0.032
hsCRP	r	-0.471	-0.466	0.405	0.405	-0.405	0.250
	p	<0.001	<0.001	<0.001	<0.001	<0.001	0.023

Table 4. ROC (Receiver operating characteristic) analysis results

Parameters	Cut-off value	Sensitivity	Specificity	P value	AUC
SH	371.93	73.3	73.2	<0.001	0.822
SS+SH	406.22	71.1	70.7	<0.001	0.796
Index 1	4.56	85.4	84.5	<0.001	0.947
Index 2	4.18	85.4	84.5	<0.001	0.947
Index 3	91.66	84.4	85.4	<0.001	0.943
IMA	0.725	97.6	97.8	<0.001	0.991

AUC: area under the curve

Table 5. Logistic regression analysis of laboratory parameters

Parameters	B	Exp (B)	95% CI for Exp (B)	Sig.
Native thiol	-0.033	0.968	0.930-1.008	<0.001
IMA	-101.423	0.001	0.001-0.001	<0.001
hsCRP	-0.016	0.984	0.853-1.135	0.004

Hosmer Lemeshow GFT: p=1.000, percentage correct=97.6%.

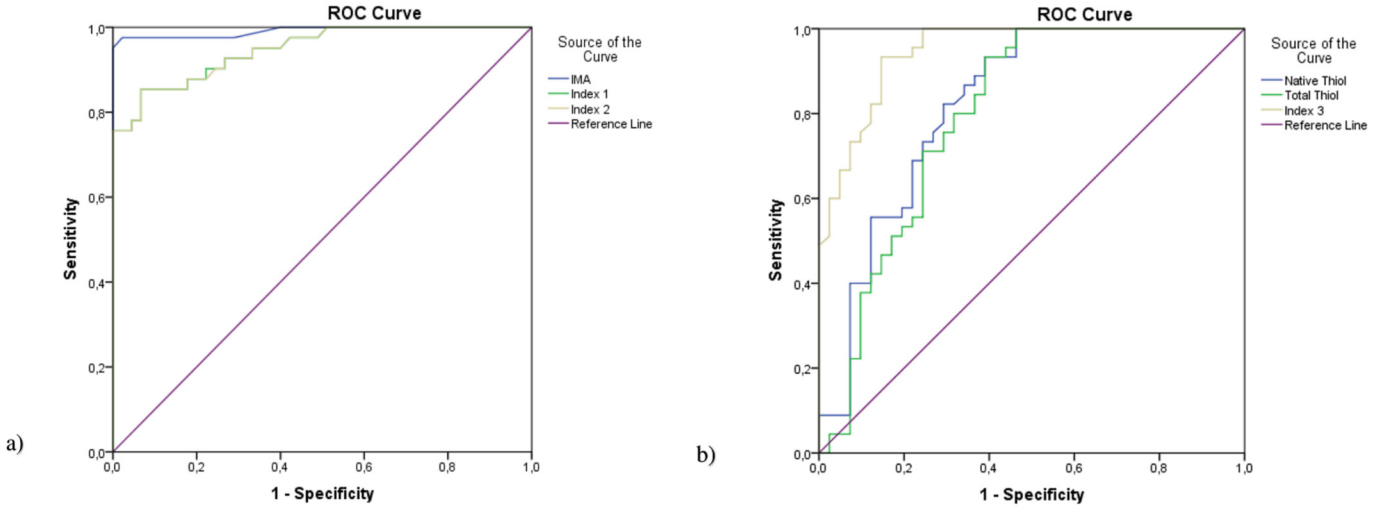

Figure 1. a) ROC curves of IMA, Index 1 and Index 2 **b)** ROC curves of Native Thiol, Total Thiol and Index 3

Discussion

In this study, SS, Index 1, Index 2, IMA, CRP and hsCRP levels were higher, SH, SS+SH and Index 3 were lower in the patient group and the difference was significant. CRP and hsCRP were positively correlated with Index 1, Index 2 and IMA, and negatively correlated with SH, SS+SH and Index 3. It was also observed that native thiol, IMA and hsCRP may be of great importance in the identification of the disease.

ROS are produced during oxygen metabolism in minute amounts and they are deactivated by antioxidant systems. An imbalance between oxidant/antioxidant species causes increased oxidative stress [12].

Thiols are free radical scavengers eliminating ROS by enzymatic and non-enzymatic mechanisms. Plasma thiol levels give us an idea about the free-radical mediated oxidation of proteins [13]. IMA is considered as a biomarker of oxidative stress, inflammation and vascular endothelial dysfunction [14]. The relationships between various diseases and DTDH with IMA impairments have been shown up to date [15-17].

IgAV, is defined as a systemic inflammatory vasculitis affecting small vessels. Among many factors listed for IgAV, oxidative stress is also listed [18]. Vascular endothelial cells are the

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primary site of vascular damage between blood stream and vessel wall [19]. When these cells are damaged, neutrophils are activated and ROS production is increased and accelerates the disease process. Leukotriene B4 (LTB4) released from activated neutrophils causes chemotaxis, aggregation and plasma exudation and also inflammation. Endothelial phospholipase A2 activation causes the degradation of arachidonic acid and this cause an increased release of tissue originated inflammatory mediators like prostaglandins, thromboxanes and leukotrienes. Besides these, anti-endothelial IgA antibodies in IgAV patients stimulate endothelial cells to release IL-8 and activate alternative complement pathway and cause release of ROS and lysosomal enzymes (elastase, collagenase) from activated neutrophiles. All of these changes triggers endothelial damage and avascular necrosis [20]. The role of oxidative damage in vasculitis pathogenesis has been evaluated in several studies [21]. Also the role of oxidative stress has been proposed to be effective in immuno-inflammatory diseases including IgAV [22].

PMNL infiltration is known to be important in IgAV pathogenesis [23]. Superoxide radicals together with H2O2 are released into extracellular fluids as a result of respiration overload of activated PMNLs. On the other hand, hypochloric acid (HOCl) is a neutrophile specific oxidant and synthesized from H2O2 and Cl− by a reaction catalyzed by myeloperoxidase (MPO). All these neutrophile derived oxidants, especially the highly toxic HOCl causes the modification of the thiol groups in proteins and may cause tissue damage [24]. In a previous study, a significant increase in neutrophile activation and oxidative stress in the active phase of IgAV has been detected while antioxidants were decreased. In another study, serum SH levels were found to be low in the beginning of the disease [25,26]. Our data have revealed that SH levels were significantly lower in especially active patient group, similar to previous reports. Native thiols are the primary target of HOCl and they are an important part of plasma antioxidant system. As albumin is the major protein exposed to oxidative stress due to MPO activity, decrease in thiol levels can be related to increased oxidation products [25]. As a result, low SH levels in IgAV patients is not only a marker for inadequate antioxidant defence mechanisms, but also a sign for protein oxidation.

In a study with IgAV patients, high levels of malondialdehyde (MDA) and low levels of total antioxidant capacity (T-AOC), superoxide dismutase (SOD), glutathione peroxidase (GSH-PX) activities were detected [20]. In another study, the role of oxidative stress in IgAV pathogenesis was evaluated with paraoxanase (PON), arylesterase (ARIL), catalase (CAT), lipid peroxidation by product MDA and serum total antioxidant status (TAS). It was found that TAS and levels of antioxidant enzymes were decreased in active IgAV patients while in remission period, PON, ARIL and TAS levels were significantly increased. Level of MDA was found to be high in active IgAV period while regressed to normal in remission period [21]. Demircin et al. had also found MDA levels to be elevated in acute phase of IgAV in a study with 16 child IgAV patient participants [27]. In yet another study, decreased SOD and GSH-PX activities and increased MDA levels were found in active IgAV patients [28]. Our data are also in concordance with these findings and show that increased oxidative stress is seen in active IgAV period and antioxidant enzymes are increased to compensate this elevation.

In a study conducted in Behçet's, a complex multisystemic inflammatory disease characterized by recurrent episodes of acute inflammation, the level of IMA increased significantly compared to the control group [29]. In addition, in another study, IMA levels were significantly increased in patients with vascular involvement compared to other patients [30]. In previous studies conducted in rheumatoid arthritis patients, IMA levels were found to be significantly higher than the control group [31]. In addition to a significant difference, another study found a correlation between IMA and disease activity score [32]. On the other hand, in a study conducted in adults with IgAV, IMA level was found to be significantly higher in patients than in the control group and in active patients compared to inactive patients [12]. All these results are consistent with the data we obtained.

To our knowledge, this is the first study to evaluate adult IgAV disease in association with serum DTDH, IMA CRP and hsCRP levels. The association between markers of oxidative stress and markers of inflammation clearly demonstrates the importance of the research. Although the small number of patients is a limitation of our study, it will take a long time for a large research group to come together as adult-onset IgAV is a very rare disease. Another shortcoming of our study is the lack of clinical scores and the inability to evaluate the oxidative stress index related to the severity of the disease. Be that as it may, this think about illustrates the part of oxidative harm in IgAV pathogenesis in grown-up IgAV. Antioxidant supplementation may be supportive of treatment in patients with active IgAV. Adult type IgAV is rare but it has a worse clinical outcome than IgAV in the childhood. So, the prevention from oxidative stress and vessel damage is more critical in the adult patient group as they will be more prone to atherosclerosis.

Conclusion

The results of the present study have revealed that oxidative stress shown by is closely related with adult IgAV disease and they are also correlated with the severity of inflammation.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
This research was affirmed by the local Institutional Review Board (approval number: E2-21-403).

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