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Assessment of Oxidative Stress and Plasma Gelsolin Levels in Children with IgA Vasculitis

Author(s)

Burcu Danacı[1], Funda Baştuğ[2], Çiğdem Karakükcü[3], Binnaz Çelik[1], Kübra Çeleğen[2]

Affiliation(s)

[1]Kayseri Training and Research Hospital, Clinic of Pediatrics, Kayseri, Türkiye

[2]Kayseri Training and Research Hospital, Clinic of Pediatrics, Division of Pediatric Nephrology, Kayseri, Türkiye

[3]Erciyes University Faculty of Medicine, Department of Biochemistry, Kayseri, Türkiye

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Abstract

Oxidative stress has been proposed to contribute to the pathogenesis of immunoglobulin A vasculitis (IgAV), but the available data remain insufficient. Our goal was to determine the role of the oxidant-antioxidant system and plasma gelsolin (pGSN) in patients with IgAV and its relationship with organ involvement. In the study, 30 individuals with IgAV diagnoses and 30 healthy controls were enrolled. All patients were examined in both the active and remission periods. Serum malondialdehyde (MDA), superoxide dismutase (SOD), and pGSN levels were measured. Compared with the remission and control groups, active IgAV patients had higher serum MDA levels; however, this difference was not statistically significant. When comparing the acute period to remission and control, serum SOD levels were somewhat lower; however, the difference was not statistically significant (>0.05). pGSN levels were prominently low in IgAV patients both in the acute and remission phases (<0.05). No correlation was found between organ involvement, serum MDA, antioxidant enzyme (SOD), and pGSN levels. Low pGSN levels in patients with IgAV may be due to pGSN consumption during the acute episode of the inflammatory process. This may tilt the delicate equilibrium between oxidants and antioxidants, potentially amplifying reactive oxygen species generation.

Keywords: IgA vasculitis, children, oxidative stress, plasma gelsolin

Introduction

Immunoglobulin A vasculitis (IgAV) is the most common vasculitis involving small vessels in childhood, and more than 90% of patients are under the age of 10 years.[1,2] IgAV can affect many tissues and organ systems, including the skin, joints, gastrointestinal system (GIS), and kidneys.[3] Although the exact cause of IgAV activation remains unknown, various substances, including nourishment, medications, antigens, pathogenic agents, and immunizations, have been linked to IgAV activation.[4] The prognosis is determined on the extent of kidney involvement, and the disease is typically self-limiting.[5]

Correspondence: Kübra Çeleğen, Kayseri Training and Research Hospital, Clinic of Pediatrics, Kayseri, Türkiye
E-mail: kubractf@hotmail.com **ORCID:** 0000-0003-2178-2788

IgA is the predominant immunoglobulin of mucosal immunity. A multi-hit hypothesis has been proposed for the pathogenesis of IgAV. Immune complexes containing galactose-deficient IgA play a central role in the pathogenesis of IgAV. Because of their large size, immune complexes containing IgA may escape hepatic degradation and accumulate in the circulation and subsequently in tissues.[6] This stimulates a widespread pro-inflammatory cascade including neutrophil activation, complement, cytokine, and chemokine secretion, the release of neutrophil extracellular traps, and increased levels reactive oxygen species (ROS). This process is believed to lead to endothelial damage and IgAV development.[6]

Oxidative stress and increased ROS production are considered one of the core mechanisms of endothelial cell injury in IgAV.[6,7] Previous studies focusing on oxidative stress in the pathogenesis of IgAV have shown elevated concentrations of malondialdehyde (MDA) in tissues, blood, and body fluids, which is used as an indicator of oxidative systems due to lipid peroxidation.[8,9] ROS also inhibits nitric oxide production in endothelial cells, damages endothelial cell DNA, and leads to apoptosis.[6] Plasma gelsolin (pGSN), which is an important actin-binding protein and regulator of cellular skeleton dynamics, has been reported to possess antioxidant and anti-apoptotic properties.[10] In inflammatory conditions such as rheumatoid arthritis, trauma, and sepsis, a decrease in pGSN levels has been observed, but its relationship with pathogenesis and therapeutic role remains unclear.[11]

Oxidative stress may contribute to the disease, but it is unclear whether it is a cause or result of the disease course.[12] Oxidative stress can also occur when antioxidant mechanisms are out of balance. There have been contradictory findings from earlier research on the contribution of oxidative stress to the pathophysiology of IgAV regarding the overall antioxidant state.[12,13] In this study, we aimed to evaluate the levels of oxidative and antioxidant enzymes, as well as pGSN, in the active and remission periods of patients with IgAV to determine their contributions to the pathogenesis of the disease. Our aim also encompassed evaluating the connection between these markers and disease activity and organ involvement.

Material and Method

Patient Selection and Demographics

This prospective case-control study was conducted on individuals diagnosed with IgAV between May 2014 and August 2015 at our hospital's pediatric nephrology unit. Patients aged 2-16 years who were diagnosed with IgAV according to the College of Rheumatology (ACR) and the European League Against Rheumatism/Pediatric Rheumatology European Society (EULAR/PReS) were included in the study.[14] Individuals were considered eligible for inclusion if they had laboratory samples available from each of the active and remission periods of the disease. Patients with chronic disease, active infection, ongoing treatment, and using nonsteroidal anti-inflammatory drugs or steroids before admission were excluded. Before enrollment in the study, informed consent was obtained from the families of all participating children. The study was approved by the Ethics Committee of our institution (date: 02.06.2017, no: 2017/296 - Erciyes University Clinical Research Ethics Committee).

Patients with IgAV diagnosis were evaluated in both active and remission periods, and laboratory samples were obtained. IgAV-active was defined as the assessment at the time the disease was first diagnosed, and IgAV-remission was defined as the 6-8 week period after the disease diagnosis. Demographics (age, sex, the presence of chronic disease, drug use, infections), and organ involvement were recorded. Following the patient selection process, a control group of healthy children who were selected from the pediatric outpatient clinic and matched the patient group in terms of average age and sex was formed. Complete blood count parameters, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), kidney and liver function tests, urine microscopy, and urine protein-creatinine ratio were studied in all patients.

Detection of Serum MDA, SOD, and pGSN Levels

Serum MDA, serum superoxide dismutase (SOD) activity, and pGSN levels were studied to assess oxidative stress in patients with IgAV and the control group for comparison. Venous blood samples (5 mL in volume) were collected from all IgAV patients before treatment. Blood samples were centrifuged, and the supernatant was stored at 800 °C.

Serum MDA levels were measured using the MDA kit (Cayman Chemical), which provides a simple, repeatable, and standardized tool for testing lipid peroxidation in plasma, serum, urine, tissue homogenates, and cell lysates. The color change formed by the reaction of MDA and thiobarbituric acid under high-temperature (90-100 °C) and acidic conditions was measured colorimetrically via a spectrophotometer at 530-540 nm. Serum SOD activity was measured using the micro ELISA method (Cayman Chemical). Using this method, total SOD activity (cytosolic and mitochondrial) was measured. pGSN levels were measured using a quantitative sandwich enzyme immunoassay method, performed using an ELISA kit (Biomatic, pGSN USA). The plate was precoated with an antibody specific to human gelsolin. The antibody could be bound to human gelsolin in the standard and samples. After washing the unbound substances in the coating, a biotinylated antibody against human gelsolin is added to the wells. In the second wash, streptavidin-horseradish peroxidase (HRP) conjugate was added. After the last wash, to remove unbound enzyme, a substrate solution (3,3',5,5'-Tetramethylbenzidine, TMB) is added to the wells, and color develops in standard solutions or in proportion to the amount of human gelsolin bound in the sample. Color development was stopped, and the intensity of the color was measured at 450 nm. Despite the logarithms of the gelsolin concentrations, the data were linearized by showing the optical density logarithms in point form. The pGSN concentration in the samples was calculated using the slope line formula.

Statistical Analysis

The analysis was performed using the Statistical Package for the Social Sciences, version 22.0 for Windows (IBM Corp., Armonk, NY, USA). QQ plots and a Shapiro-Wilk test were used to analyze the normal distribution of parametric data. For discrepancies between the IgAV-active and IgAV-remission parameters, a dependent sample t-test (paired sample t-test) was used. The patient and control groups were compared using an independent sample t-test, and the findings are presented as mean ± standard deviation. Variance homogeneity was examined using the Levene test. Correlations between parameters were evaluated using either the Pearson or Spearman coefficient. A p-value 0.05 was considered statistically significant.

Highlights

- Increased generation of reactive oxygen species and consequential oxidative stress are recognized as fundamental mechanisms underlying endothelial cell injury in immunoglobulin A vasculitis (IgAV).
- Plasma gelsolin (pGSN) is a protein known for its antioxidant and anti-apoptotic properties, which was found to be prominently low in both the active and remission phases of IgAV.
- The reduced amount of pGSN in patients with IgAV may be attributed to its consumption during the acute episode of the inflammatory process.

Results

The IgAV group included 19 boys (63%) and 11 (37%) girls, and the control group included 12 boys (40%) and 18 girls (60%) (p=0.07). No significant difference was noted in the mean age between the patient and control cohorts (9.21±4 vs. 8±3.8; p=0.25). At the first admission, all IgAV patients had palpable purpura, 25 of the patients (83.3%) had articular purpura, 17 (56.6%) had gastrointestinal purpura, three patients had kidney (10%) and scrotal involvement (10%). One patient developed scalp edema. Of all patients with joint involvement, nonsteroidal anti-inflammatory medications (n=15; 50%) were used in their treatment. Steroid treatment was administered to 15 (50%) patients with scalp edema, scrotal edema, GIS involvement, and renal involvement. In follow-up, remission was achieved in all patients in an average of 6-8 weeks, but one of the patients with GIS and kidney involvement went into remission after approximately 5 months with high-dose steroid treatment.

Table 1 displays the biochemical analyses of the subjects. The mean leukocyte number, platelet count, and CRP levels were significantly higher in the IgAV-active group than in the IgAV-remission and control group (<0.05). ESR levels in the IgAV active and remission groups were much greater than those in the control group <0.05. In comparison with the control group, the IgAV-active and remission groups had significantly decreased serum albumin levels (<0.05).

Oxidative biomarker levels of the groups are demonstrated in **Table 2**. Children with active IgAV had greater MDA levels than those in the remission and control groups, although this difference was not statistically significant. No correlation was observed between ESR, CRP levels, and MDA levels. SOD levels were slightly lower in the acute phase compared with those in remission and control, but it was not significantly different (>0.05). In comparison to the control group, the IgAV-active and -remission groups had significantly reduced pGSN levels. (Median pGSN IgAV-active vs IgAV-remission; p=0.021, IgAV-active vs. control p=0.003, IgAV-remission vs. control p=0.006). There was no relationship between age and sex and pGSN levels (>0.05). There was no correlation between inflammatory markers and pGSN levels (ESR; r=0.206, p=0.36, CRP; r=-0.09, p=0.68). As shown in **Table 3**, no significant relationship was found between organ involvement, serum MDA, SOD, and pGSN levels.

Discussion

Understanding the pathogenesis of IgAV is essential for the development of appropriate therapies. The pathogenesis of IgAV has been the subject of many theories. However, none have been clarified. The pathophysiology of IgAV is also believed to involve oxidative damage and lipid peroxidation. In this study, lipid peroxidation, an antioxidant enzyme, and pGSN levels in patients diagnosed with IgAV were investigated. pGSN levels in IgAV patients were observed to be considerably lower than those in controls, particularly during the acute phase.

Oxidant molecules produced by various reactions are neutralized by natural antioxidant molecules that are always present at certain levels in the body.[13] Oxidative stress is the disruption of the existing balance that releases free radicals and ROS, resulting in the activation of inflammatory cells and endothelial damage. Elevated levels of ROS can exert direct cytotoxic effects and impact mitochondrial respiration, thereby inducing lipid peroxidation in the cell membrane.[6] MDA arising from membrane lipid peroxidation is considered indicative of the extent of endothelial cell damage. In previous studies, elevated serum MDA levels were demonstrated in the acute phase of IgAV.[13,15,16] Zhu et al.[17] demonstrated a positive correlation between serum MDA levels and the degree of pathological grade in IgAV nephritis patients. Their findings suggest that the intensity of the inflammatory response and oxidative stress are closely related to the seriousness of the disease in IgAV.[17] In the current study, higher serum MDA levels were found in patients with IgAV in the active and remission phases compared with controls, but the difference was not significant. In addition, no correlation was observed between MDA levels and organ involvement. In agreement with our results, Kisaoglu et al.[12] found no difference in serum MDA levels between acute and remission phases in patients with IgAV. In both of these latter studies, no association between lipid peroxidation and IgAV activity and organ involvement was demonstrated, but this may be because the participants had mild diseases.

The following damage to vascular endothelial cells, neutrophils are stimulated and produce huge amounts

Table 1.
Comparison of laboratory parameters of the IgAV-active, IgAV-remission, and control groups

Variables	IgAV-active n=30	IgAV-remission n=30	Control n=30	IgAV-active vs. IgAV-remission	IgAV-active vs. control	IgAV-remission vs. control
				p*	p#	p#
HGB (g/dL)	13.2±1.5	13.5±1.3	12.8±0.7	0.33	0.19	0.02
MCV (fL)	82.1±5.1	82.2±5.4	81.2±5.1	0.77	0.52	0.48
WBC (/mm^3)	9763.7±2729	7821.7±3806	7016.7±2599	**0.006**	**<0.001**	0.09
PLT (x10^3/mm^3)	379±88	338±90	334±52	**0.003**	**0.02**	0.84
MPV (fL)	8.83±0.93	8.92±0.97	9.81±0.6	0.34	0.93	0,60
ESR (mm/h)	13.43±9.96	8.06±7.95	4.13±3.83	**0.007**	**<0.001**	**0.02**
CRP (mg/L)	22.16±22.64	5.62±6.79	3.45±0.75	**<0.001**	**<0.001**	0.09
Protein (g/dL)	6.76±0.67	6.74±0.52	7.16±0.45	0.83	**0.01**	**0.001**
Albumin (g/dL)	3.87±0.49	4.26±0.33	4.5±0.34	**<0.001**	**<0.001**	**0.009**

Statistically significant results (p<0.05) are shown in bold
*: Data were analyzed using the paired t-test.
#: Data were analyzed using an independent sample t-test
IgAV; Immunoglobulin A vasculitis, HGB; Hemoglobin, MCV; Mean corpuscular volume, WBC; White blood cell count, PLT; Platelet count, MPV; Mean corpuscular volume, CRP; C-reactive protein, ESR; Erythrocyte sedimentation rate

Table 2.
Comparison of oxidative stress biomarkers between the IgAV-active, IgAV-remission, and control groups

Variables	IgAV-active n=30	IgAV-remission n=30	Control n=30	IgAV-active vs. IgAV-remission	IgAV-active vs. control	IgAV-remission vs. control
				p*	p#	p#
MDA (µmol/L)	11.408±3.254	10.138±2.367	10.030±2.467	0.10	0.07	0.86
SOD (U/mL)	4.9±2.3	4.7±1.9	5.2±2.3	0.35	0.67	0.35
pGSN (µg/mL)*	104.5±72.1	74.8±50.97	265.1±257.4	**0.021**	**0.003**	**0.006**

Statistically significant results (p<0.05) are shown in bold
*24 patients
*: Data were analyzed using the paired t-test
#: Data were analyzed using an independent sample t-test
IgAV; Immunoglobulin A vasculitis, MDA; Malondialdehyde, SOD; Superoxide dismutase, pGSN; Plasma gelsolin

Table 3.
Comparison of serum MDA, SOD, and pGSN levels according to joint involvement, GIS involvement, and renal involvement

		Joint involvement			GIS involvement			Renal involvement		
Variables	**Involvement**	**n**	**Mean ± SD**	**p**	**n**	**Mean ± SD**	**p**	**n**	**Mean ± SD**	**p**
MDA	Yes No	25 5	11.09±3.07 12.98±4.03	0.24	17 13	10.97±3.07 11.97±3.51	0.41	3 27	10.16±3.2 11.54±3.28	0.49
SOD	Yes No	25 5	4.83±2.23 5.52±2.63	0.54	17 13	4.92±2.4 4.96±2.18	0.96	3 27	4.02±0.68 5.04±2.36	0.47
pGSN	Yes No	21 3	99.8±75.2 137.1±35.4	0.41	14 10	106.8±47.9 101.3±87.1	0.85	3 21	82.1±75.5 107.7±72.9	0.57

MDA; Malondialdehyde, SOD; Superoxide dismutase, pGSN; Plasma gelsolin, GIS; Gastrointestinal system, SD; Standard deviation

of ROS that further favor the progression of IgAV. The maintenance of a dynamic balance between the generation and removal of ROS depends on the antioxidant enzyme systems.[8] In comparison with healthy controls, Zhu et al.[17] found that patients with IgAV had significantly decreased levels of antioxidant enzymes (SOD and total antioxidant capacity) throughout the acute phase. They discovered that individuals with organ involvement and IgAV with nephritis had considerably decreased antioxidant enzyme activity.[17] Consistent with our research findings, Demircin et al.[15] demonstrated that serum SOD levels were slightly lower in the acute phase than in the remission phase, but this difference was not statistically significant. In addition, another study reported significantly lower levels of SOD and glutathione peroxidase in the early time of IgAV than in the remission phase. While a notable increase in the activities of antioxidant enzymes was noted during remission, their levels persisted below those observed in the control group.[16] Ece et al.[13] demonstrated a lower total antioxidant status and arylesterase activity in active patients compared with the control and remission phases. Furthermore, there were no appreciable variations between the active and remission phases of other antioxidant enzymes, such as catalase and paraoxonase; however, their levels were lower in the treated group than in the control group.[13] Compared with remission and control, SOD levels were lower in the active phase but not statistically significant in our study. The small number of patients with nephritis in our study may be the reason for the difference between these enzyme levels.

Cytoplasmic gelsolin is an important component of cellular dynamics; it is an actin-regulating protein required for phagocytosis and cell motility, and it also has antibacterial and anti-inflammatory qualities.[18]

The extracellular gelsolin isoform is called pGSN, and its physiological relevance remains unknown. In infectious and inflammatory conditions, such as sepsis,[19] rheumatoid arthritis,[20] and multiple sclerosis,[21] pGSN levels are markedly low. Simultaneously, gelsolin-actin complexes have been observed in the synovial fluid of patients with rheumatoid arthritis.[22] In an IgA nephropathy model, Han et al.[18] reported lower pGSN levels in serum and increased deposition of GSN in mouse kidneys. This finding was validated in a human study where serum levels of IgA nephropathy patients were significantly lower than those of patients with other glomerular disorders and healthy controls.[23] They also showed an association between higher renal tissue GSN levels and mesangial proliferation and sclerosis according to the Oxford classification.[23] A later *in vitro* investigation revealed that GSN aided in cell mitosis, which in turn enhanced the proliferation of human mesangial cells.[23]

Of the available studies, only one investigated the role of pGSN in individuals with IgAV, revealing diminished pGSN levels during the active period of IgAV in comparison with those in healthy controls.[24] In the current study, pGSN levels were measured in patients with IgAV during both active and remission periods, and the results were compared with those of controls. The pGSN levels were also considerably low during the active and remission periods and were much more pronounced during the remission period. pGSN levels did not correlate with organ involvement in this study. This may be due to the use of pGSN in the acute phase of the inflammatory process and its continuation until the disease was in remission. There was no discernible association between the levels of pGSN and markers indicating active inflammation. On the other hand, a reduction in pGSN could lead to an imbalance between oxidative enzymes and an increase in ROS levels.[18] It's not clear whether the illness process is caused or impacted by pGSN levels.

Study Limitations

Our study has some limitations. Our study was conducted with a small patient population. Therefore, oxidant and antioxidant enzyme levels in patients with IgAV, which were found to be significantly different in previous studies, may not have differed from the control group in this research. Compared with earlier research, fewer individuals in our study had severe illness and nephritis. This may have limited our evaluation of the relationship between organ involvement and oxidative stress markers. Despite these limitations, we assessed patients in both active and remission phases and compared them with the enzyme levels in healthy individuals.

Conclusion

In summary, to the best of our knowledge, this is the first well-designed study comparing the levels of pGSN in patients with IgAV during both the early and remission stages. IgAV is a systemic inflammatory disease, and the role of oxidant and antioxidant systems is important in its pathogenesis. The diminished plasma levels of GSN observed in patients with IgAV suggest a contribution of this protein to the pathogenesis. To better understand the connection between oxidative stress, pGSN, and IgAV pathogenesis, further research is required.

Ethical Approval: The study was approved by the Ethics Committee of our institution (date: 02.06.2017, no: 2017/296 - Erciyes University Clinical Research Ethics Committee).

Informed Consent: Before enrollment in the study, informed consent was obtained from the families of all participating children.

Author Contributions: Danacı B: Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Baştuğ F: Concept, Design, Data Collection or Processing, Literature Search, Writing. Karakükcü Ç: Surgical and Medical Practices, Writing.; Çelik B: Data Collection or Processing, Literature Search, Writing.; Çeleğen K: Analysis or Interpretation, Literature Search, Writing.

Conflict of Interest: The authors have no conflicts of interest to declare.

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