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ORIGINAL ARTICLE

Relationship between IgA vasculitis and prothrombotic risk factors: A prospective, case-control study

Cengiz Zeybek[1], Ahmet Bolat[2], Orhan Gürsel[3], Bülent Hacıhamdioğlu[4], Ahmet Emin Kürekçi[5]

[1]Division of Pediatric Nephrology, University of Health Sciences, Gülhane Medical Faculty, Ankara, Türkiye
[2]Department of Pediatrics, University of Health Sciences, Gülhane Medical Faculty, Ankara, Türkiye
[3]Division of Pediatric Hematology, University of Health Sciences, Gülhane Medical Faculty, Ankara, Türkiye
[4]Division of Pediatric Endocrinology, Medical Park Hospital, Istanbul, Türkiye
[5]Division of Pediatric Hematology, Lösante Hospital, Ankara, Türkiye

Correspondence: Cengiz Zeybek, MD.
E-mail: zeybekcengiz@yahoo.com

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ABSTRACT

Objectives: This study aimed to determine whether there are commonly occurring hematologic causes that may lead to thrombosis in patients recently diagnosed with immunoglobulin A vasculitis (IgAV).

Patients and methods: The prospective study enrolled 107 pediatric patients diagnosed with IgAV and 98 healthy age- and sex-matched controls. Patients with IgAV who were treated at a single center between February 2016 and June 2022 were evaluated for the prevalence and clinical relevance of thrombophilic gene mutations and other prothrombotic risk factors, as well as coagulation test indices. The genotypes for common mutations in prothrombin (Pt) G20210A, factor V Leiden (FVL), and methylenetetrahydrofolate reductase (MTHFR) C677T were assessed. The coagulation assays, including Pt time and activated partial thromboplastin time, and the levels of fibrinogen, factor VIII, factor IX, and von Willebrand factor antigen were analyzed. Additionally, the levels of antithrombin, protein C, and free protein S were evaluated during the disease's acute phase before initiation of anti-inflammatory drugs.

Results: Seventeen of the 107 IgAV patients were excluded. Consequently, 90 children (36 males, 54 females; mean age: 10.2±3.2 years; range, 3 to 18 years) diagnosed with IgAV and 98 healthy children (45 males, 53 females; mean age: 9.7±3.8 years; range, 2 to 18 years) as a control group were analyzed. A statistical analysis found no significant difference between the groups in terms of indices of coagulation assays and other prothrombotic risk factors ($p>0.05$). The mutation frequencies of the Pt G20210A, FVL, and MTHFR C677T loci among IgAV patients were not significantly different from the control group ($p>0.05$).

Conclusion: Given there is no predisposition to thrombophilia and IgAV is a form of vasculitis, the cause of thrombosis among patients with IgAV may involve mechanisms related to the inflammation-hemostasis cascade.

Keywords: Children, immunoglobulin A vasculitis, thrombophilia, thrombosis.

Immunoglobulin A vasculitis (IgAV) is the leading form of vasculitis among children, marked by the deposition of immunoglobulin A1-dominant immune complexes on small vessel walls. Apart from skin involvement characterized by typical anaphylactoid purpura lesions in the lower extremities, gastrointestinal tract, joint, and kidney involvement may also develop among patients with IgAV.[1] Although rare, thrombosis has been encountered in patients with IgAV. This complication is usually described in case reports of children.[2-9] Thrombosis in these patients has frequently been reported as intracardiac, deep venous, and arterial thrombosis in the lower extremities, superior mesenteric artery thrombosis, cerebral vein thrombosis, and superior sagittal or central venous thrombosis. Thrombosis has also been observed in adults with IgAV, and the sites of thrombosis in these patients include the dorsal penile vein, portal vein, and coronary arteries.[10-12] However, no common hematological cause of thrombosis has been found in these cases.

These observed cases raise the question of whether patients with IgAV have a hematological predisposition to thrombosis. Despite having conducted some studies to investigate this question, the literature contains only a few studies on common thrombophilic gene mutations, including factor V Leiden (FVL), prothrombin (Pt) G20210A gene, and the C677T genetic variant of the methylenetetrahydrofolate reductase (MTHFR) gene in patients with IgAV.[13] This study aimed to ascertain a common hematological problem that may cause thrombosis in patients with newly diagnosed IgAV by searching not only thrombophilic gene mutations but also coagulation test indices (Pt time [PT] and activated partial thromboplastin time [aPTT]) and the activity of antithrombin (AT), protein C (PC), free protein S (PS), fibrinogen, factor VIII, factor IX, and von Willebrand factor antigen (vWF:Ag).

PATIENTS AND METHODS

The prospective, case-control study was performed in the pediatric outpatient clinic of the Gülhane Research and Training Hospital between February 2016 and June 2022. The IgAV diagnosis was made based on the classification criteria developed by EULAR (European Alliance of Associations for Rheumatology)/PRINTO (Paediatric Rheumatology International Trials Organisation)/PRES (Paediatric Rheumatology European Society).[14] One hundred seven children diagnosed with IgAV comprised the case group, and 98 healthy children constituted the controls. A group of healthy children who were not taking any medication and who presented themselves to the hospital for routine follow-up exams were included in the control group. These children had normal blood and urine tests, and they did not have vasculitis or hematological problems. The exclusion criteria for both groups were as follows: antiplatelet drug use in the last 30 days; hematologic disease; chronic heart, kidney (including nephrotic or nephritic range proteinuria in the case group because this can cause hypercoagulability), or liver disease; polycythemia; or an individual/family history of thrombosis. Both groups underwent assessment for factor VIII, factor IX, PC, free PS, AT, PT, aPTT, fibrinogen, vWF:Ag, complement 3, immunoglobulin A, serum albumin, serum creatinine, and C-reactive protein levels, white blood cell count, erythrocyte sedimentation rate, and Pt G20210A, FVL, and MTHFR C677T gene mutations. The study protocol was approved by the Gülhane Military Medical Academy Ethics Committee (date: 08.01.2016/1491-1078-16/1539). Written informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Antecubital vein-derived peripheral blood was collected into EDTA vacutainer tubes for mutational analysis, while some blood was collected 3.8% trisodium citrate vacutainer tubes for other examinations at the disease's acute phase before starting nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids. Through the use of a QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany), DNA was isolated from blood samples. These samples were then kept at –20°C for polymerase chain reaction (PCR). Polymorphism screening was done using the SNaPshot multiplex system (Applied Biosystems, Waltham, MA, USA). Three initial sets of primers were created for each of the three genetic variations: two for PCR and one for the SNaPshot assay. The agarose gel electrophoresis method was employed to perform the PCR analyses. The NucleoFast 96 PCR kit (MACHEREY-NAGEL GmbH & Co. KG, Düren, Germany) was used to amplify the PCR products for the samples.

Prothrombin time, aPTT, fibrinogen, factor VIII, factor IX, PC, free PS, vWF:Ag, and AT were measured with a coagulometry analyzer (STA Compact Coagulometry Analyser; Diagnostica Stago, Asnières-sur-Seine, France). Biochemical values were obtained using an automated chemistry analyzer (AU680; Beckman Coulter, Brea, CA, USA), while complete blood counts were determined using an automated hematology analyzer (Beckman Coulter, Brea, CA, USA).

Statistical analysis

G*Power version 3.1.9.2 software (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) was used for the sample size calculation. To guarantee a statistically significant difference

between groups with an effect size of d=0.50, a type 1 error rate alpha (α) of 0.05, and a power of 0.90, a minimum of 86 participants was required, as determined by the results of a comparable published study.[15]

The IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA) was utilized to carry out the analysis. The Kolmogorov-Smirnov test was employed to assess if distribution was normal. All of the continuous variables followed a normal distribution, and data was reported in terms of the mean ± standard deviation (SD). Normally-distributed variables were evaluated using parametric tests. To investigate the continuous variables that were present in both of the separate groups, an independent sample t-test was utilized. The chi-square test was utilized to assess categorical data, which were displayed as frequency and percentage. A p-value <0.05 was considered statistically significant.

RESULTS

Figure 1 is a flowchart that illustrates the course of the investigation. Twelve individuals were excluded from the study due to their usage of NSAIDs upon admission to our clinic, and two patients declined to take part in the research. Thus, the study included 90 patients (36 males, 54 females; mean age: 10.2±3.2 years; range, 3 to 18 years). None of the participants in the control group were excluded from the study (n=98; 45 males, 53 females; mean age: 9.7±3.8 years; range, 2 to 18 years).

Table 1 displays the case and control group demographic specifications. It was found that there was no significant difference between case and control groups in terms of age, sex, or blood pressure (p>0.05). In addition to purpura, which was seen in all patients in the case group, joint and bowel involvement was particularly common (71.1% and 53.3% of patients, respectively). NSAIDs were used in patients with joint involvement, and steroids were used in patients with bowel involvement. At the time of presentation, four (4.4%) subjects had microscopic hematuria. No patient had gross hematuria, and none of the patients experienced recurrent IgAV.

No statistically significant differences were observed between groups for PT, aPTT, fibrinogen,

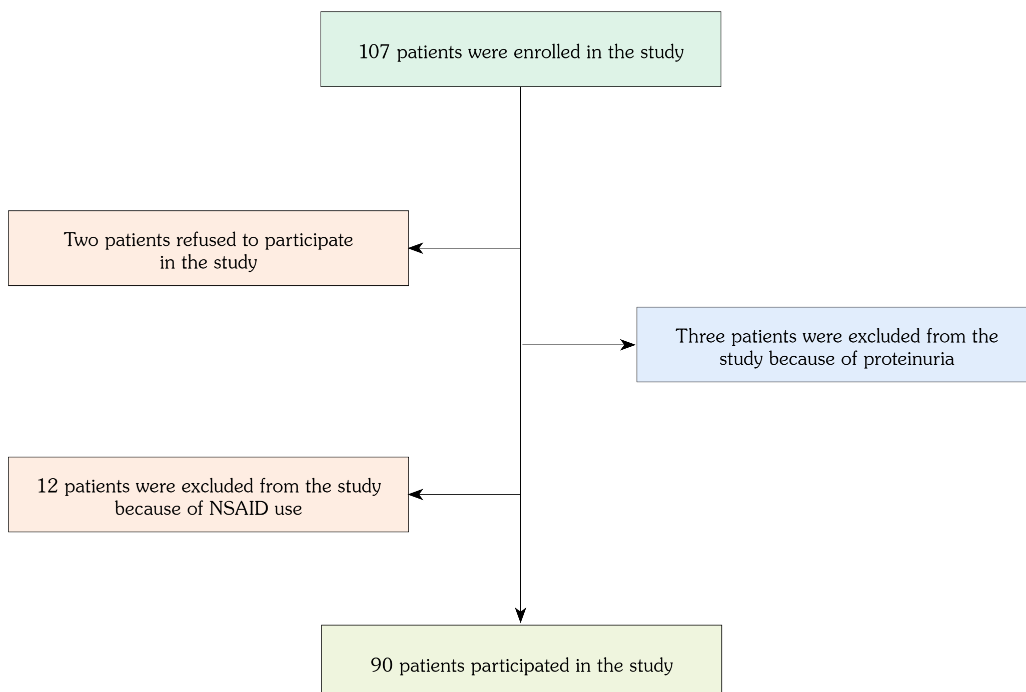

Figure 1. Flow diagram showing the progress of patients through the study.
NSAID: Nonsteroidal anti-inflammatory drug.

Table 1. Demographic characteristics of patients in the case and control groups

	Case group (n=90)			Control group (n=98)			
Participant characteristics	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			10.2±3.2			9.7±3.8	0.47
Sex							0.63
Female	54	60		53	54.1		
Male	36	40		45	45.9		
SBP (mmHg)			110±10			110±15	0.61
DBP (mmHg)			70±5			65±5	0.38
Purpuric rash	90	100	–	–	–		
Joint involvement	64	71.1	–	–	–		
Bowel involvement	48	53.3	–	–	–		

SD: Standard deviation; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

PC, free PS, AT, factor VIII, factor IX, vWF:Ag, or other routine laboratory values (p>0.05; Table 2). None of the patients in the case group had prothrombotic risk factors (decreased AT, PC, and free PS levels or increased factor VIII, factor IX, vWF:Ag, and fibrinogen levels). A comparison between the groups revealed that the case group had a slightly higher white blood cell count and acute phase reactants (erythrocyte sedimentation rate and C-reactive protein; p>0.05).

Table 3 displays the Pt G20210A, FVL, and MTHFR C677T variants in the case and control

Table 2. Distribution of hematological data of the case and control groups

	Case group (n=90)	Control group (n=98)	
	Mean±SD	Mean±SD	*p*
PT (sec)	13.56±0.13	13.68±0.19	0.58
aPTT (sec)	29.80±0.27	30.08±0.28	0.25
Fibrinogen (mg/dL)	288±6.20	295±7.88	0.89
PC activity (%)	96.37±16.89	99.88±17.97	0.79
Free-PS activity (%)	100.91±22.84	104.14±24.63	0.51
AT activity (%)	103.66±10.51	100.18±9.78	0.67
Factor VIII (%)	84.87±23.86	91.98±25.41	0.18
Factor IX (%)	86.63±14.46	96.63±22.64	0.21
vWF:Ag (%)	88.29±24.73	94.48±29.53	0.35
WBC (10^9/L)	10.51±5.21	8.97±6.35	0.18
C3 (g/L)	1.21±0.26	1.41±0.37	0.25
IgA (g/L)	1.97±0.83	2.09±0.91	0.31
Serum albumin (g/L)	40.72±6.23	37.58±7.11	0.44
Serum creatinine (mg/dL)	0.47±0.24	0.42±0.28	0.77
ESR (mm/h)	20±13	17±11	0.22
CRP (mg/dL)	1.22±0.15	1.01±0.08	0.17

SD: Standard deviation; PT: Prothrombin time; aPTT: Activated partial thromboplastin time; PC: Protein C; free-PS: Free protein S; AT: Antithrombin; vWF:Ag: von Willebrand factor antigen; WBC: White blood cell; C3: Complement 3; IgA: Immunoglobulin A; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein.

Table 3. Prothrombin gene (G20210A), FVL, MTHFR (C677T) mutations in the case and control groups

	Case group (n=90)		Control group (n=98)		
Parameters	n	%	n	%	*p*
FVL					0.76
Wild type (GG)	82	91.1	88	89.8	
Heterozygous (AG)	8	8.9	10	10.2	
Homozygous (AA)	0	0	0	0	
Total mutation	8	8.9	10	10.2	
Pt G20210A					0.47
Wild type (GG)	90	100	96	98	
Heterozygous (AG)	0	0	2	2.0	
Homozygous (AA)	0	0	0	0	
Total mutation	0	0	2	2.0	
MTHFR C677T					0.51
Wild type (CC)	52	57.8	54	55.1	
Heterozygous (CT)	36	40	42	42.9	
Homozygous (TT)	2	2.2	2	2.0	
Total mutation	38	42.2	44	44.1	

Pt G20210A: Prothrombin gene G20210A; FVL: Factor V leiden; MTHFR: Methylenetetrahydrofolate reductase; GG: Guanine- guanine; AG: Adenine-guanine; AA: Adenine-adenine; CC: Cytosine-cytosine; CT: Cytosine-thymine; TT: Thymine-thymine.

groups. In the case and control groups, FVL was detected at frequencies of 8.9% and 10.2%, respectively, while Pt G20210A was found at frequencies of 0.0% and 2.0%, respectively. Participants in the case group (40%) and controls (42.9%) were heterozygous for MTHFR C677T, and no statistical significance was found between the two groups (p>0.05). Two subjects in each group were homozygous for MTHFR C677T (patients with hyperhomocysteinemia were treated with folic acid). There were no notable genotypic differences in the frequencies between the groups (p>0.05). Thrombosis was not observed in patients with FVL and MTHFR C677T mutations in the case group during the study.

DISCUSSION

This study assessed the risk of thrombosis among pediatric patients with IgAV in comparison to a control group. As a result, no significant differences with regard to thrombophilic gene defects, coagulation test indices, or other prothrombotic risk factors were determined between the groups.

Immunoglobulin A vasculitis is a usually self-limiting, systemic, nongranulomatous form of small vessel vasculitis. Its prognosis in most children is excellent, with spontaneous resolution of signs and symptoms.[16] There have been a few reports of thrombosis in children with IgAV.[2-9] ATIII deficiency, MTHFR gene polymorphism, increased lipoprotein A, homocysteine, factor VII levels, and antiphospholipid antibody test positivity have been shown to cause thrombosis in these patients.[3-9] In some cases, however, no hematological cause was found.[2]

Twelve patients were excluded from the current investigation due to NSAID use, as it is linked to an elevated risk of venous thromboembolism (VTE).[17] The cause has not been fully elucidated, but thromboxane-prostacyclin imbalance may be a contributing factor.[18] Inhibition of prostacyclin synthesis by these NSAIDs may increase platelet aggregation.

The vWF:Ag level has been proposed to be a potential marker for endothelial cell injuries.[19] A study comprising 258 patients found that the factor VIII-related antigen (vWF) level was elevated in patients who had systemic necrotizing arteritis and large vessel arteritis, but not among patients who had small vessel vasculitis, including IgAV.[20] Conversely, it has been shown that vWF:Ag may be a specific marker for monitoring disease activity among patients who had small vessel vasculitis.[21] When we compared both groups in terms of

vWF:Ag levels, we discovered that there was no statistically significant difference between them.

The results of routine coagulation tests are usually normal in patients with IgAV.[22] However, some studies with hematologic abnormalities have also been reported. For example, a few studies of patients with IgAV have shown a slight decrease in factor XIII levels and capillary resistance, as well as disturbed qualitative functioning of platelets.[23,24] Besbas et al.[25] showed that plasma endothelial injury/activation and fibrinolysis markers were increased in patients with acute-phase IgAV. Yılmaz et al.[26] examined the platelet ristocetin cofactor, thrombin/AT complex, Pt fragments 1 and 2, vWF:Ag, and fibrinogen in patients with acute-phase and recovery-phase IgAV and compared them with 79 healthy controls. Compared to patients with recovery-phase IgAV and the controls, the procoagulant levels in the acute-phase IgAV patients were considerably greater. However, no change was detected in the levels of natural anticoagulants such as PC, free PS, and AT, similar to our study. Their study showed that patients with IgAV at an acute phase were in a hypercoagulable state. Additionally, Brendel-Müller et al.[27] showed that the coagulation system was activated during the disease's acute phase. However, the retrospective methodology, limited patient population (only 17 patients), and absence of a control group were the limitations of the study. Interestingly, Brendel-Müller et al.[27] administered heparin to some of their patients because they detected hypercoagulability; however, this treatment did not affect the progression of the disease. In the study conducted by Prandota et al.,[28] 14 patients with IgAV were compared to a control group. The researchers discovered that the patients with IgAV had significantly increased concentrations of plasma plasminogen and fibrinogen. Their study also suggested impaired activation of the fibrinolytic system among IgAV patients. Contrary to these studies, we did not detect a hypercoagulable state in the patients who had IgAV.

It is possible that the factor XIII deficiency in patients with IgAV is associated with a more severe progression of the disease as well as gastrointestinal complications.[22,27,29] It has even been reported that factor XIII replacement therapy can be used to treat gastrointestinal system complications.[22] The proteases released from inflammatory cells, particularly in the perivascular tissue of the small intestine, cause excessive consumption of factor XIII.[30] However, a recent study has raised questions about the efficacy of this treatment modality.[29] Factor XIII has not been reported in the literature as a cause of thrombosis in IgAV. This may be because factor XIII deficiency increases the tendency to hemorrhage rather than thrombosis.

Similar to our study, Dagan et al.[13] compared FVL, Pt G20210A, and MTHFR gene C677T mutations in 52 IgAV patients and 104 controls, and they found no differences between the two groups. However, unlike in our study, they did not examine other prothrombotic risk factors, and the control group consisted of adults. Nevertheless, neither our study nor theirs showed any significant differences in thrombophilia gene defects between the two groups.

Since IgAV is a small vessel vasculitis and inflammation shifts hemostatic activity to a procoagulant state via proinflammatory mediators, it is possible that the inflammatory process is the basis of thrombosis in these patients.[31,32] Additionally, patients with vasculitides other than IgAV have undergone thrombophilia gene studies. For example, a comparison was made between 79 patients diagnosed with Behçet's disease and a healthy control group in terms of AT, PC, free PS, FVL, Pt G20210A, MTHFR C677T polymorphisms, and acquired thrombophilic risk factors, including anticardiolipin antibodies, lupus anticoagulant, and the levels of serum homocysteine, but no observable differences were documented.[15] The occurrence of thrombosis among patients diagnosed with Behçet's disease has been linked to a reduction in nitric oxide (NO) as a result of endothelial dysfunction. This is due to the fact that NO induces vasodilation and inhibits platelet aggregation.[33] However, conflicting results were found in studies on NO polymorphisms in patients with IgAV.[34,35] Another possible reason for the likelihood of thrombosis among patients diagnosed with Behçet's disease is increased numbers of activated platelets and platelet microparticles, which can trigger the coagulation cascade.[36,37] One study on ANCA (antineutrophil cytoplasmic antibody)-associated vasculitis, which can cause VTE, found no

mutations in FVL, and PC, free-PS, AT, and antiphospholipid antibody levels were normal in all patients who developed VTE.[38] In another study, no relationship was found between granulomatosis with polyangiitis and common genetic prothrombotic disorders, such as FVL, Pt G20210A, or MTHFR gene mutations.[39] The secretion of neutrophil extracellular traps (NETs) has been associated with increased risk of thrombosis in ANCA-related vasculitis.[40] A study demonstrated that NETs were released into the circulation of patients with IgAV and were implicated in disease activity.[41] Among patients with Kawasaki disease, another form of vasculitis, CD40 ligand (CD40L) expression was found to be increased in both CD4-positive T cells and platelets, and this was associated with the occurrence of coronary artery thrombosis.[42] Activated platelets may act as proinflammatory cells in inflammation in patients with vasculitides.[43] Platelet activation releases many cytokines, including CD40L and P-selectin.[44,45] P-selectin leads to thrombus growth via tissue factor-rich microparticles.[46] Studies in primates have shown that inhibition of P-selectin leads to thrombus resolution comparable to the effect of enoxaparin.[47] A few studies in patients with IgAV have shown both P-selectin gene polymorphisms and increased P-selectin expression at the tissue level in the acute phase.[48]

This study had three main limitations. First, it is possible that the small sample size made it impossible to assess the presence of thrombophilia in IgAV patients. Second, studies involving methods such as the thrombin generation test, which shows a much higher tendency toward thrombosis, could not be performed due to their cost. Third, no patients in our case group had obvious thrombosis. Whether subclinical thrombosis developed in our case group remains unknown. The strength of our study is that it is the first investigation that evaluates coagulation test indices, additional prothrombotic risk factors, and thrombophilia gene mutations simultaneously in children diagnosed with IgAV.

In conclusion, we found no significant difference in thrombophilic gene mutations, coagulation test indices, and other prothrombotic risk factors between groups. Nevertheless, considering that IgAV is a form of vasculitis, thrombosis in patients with IgAV may be associated with factors such as NO, platelet microparticles, NETs, CD40L, and P-selectin, which are involved in the coagulation-inflammation cascade. Therefore, further studies of such markers are needed.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Came up with the study's concept and design: C.Z., A.B., O.G., B.H., A.E.K.; The data collection was carried out: O.G., B.H., A.E.K.; Were responsible for analyzing and interpreting the results: C.Z., A.B., O.G.; The initial draft of the paper was prepared: C.Z., A.B., O.G., A.E.K. The results were evaluated by all authors, who then approved the final version of this manuscript.

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