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INCIDENCE OF THROMBOEMBOLIC EVENTS IN PATIENTS WITH A SYSTEMIC FORM OF VASCULITIS AND CUTANEOUS VASCULITIS

UČESTALOST TROMBOEMBOLIJSKIH DOGAĐAJA U SISTEMSKOM OBLIKU VASKULITISA I LOKALIZIRANOM KOŽNOM VASKULITISU

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Sažetak

Uvod: Vaskulitis je rijetka bolest karakterizirana upalom i nekrozom krvnih žila. Upalom inducirana tromboza smatra se svojstvom nekoliko autoimunosnih bolesti poput sistemskog eritemskog lupusa (SLE), reumatoidnog artritisa (RA), Sjögrenova sindroma (SS) te sistemskih vaskulitisa. U ovom istraživanju nastojali smo utvrditi učestalost tromboembolijskih (TE) događaja kod sistemskog oblika vaskulitisa i vaskulitisa ograničenog na kožu te procijeniti koji su mogući rizični čimbenici za razvoj tromboembolijskih (TE) događaja. *Ispitanici i metode:* U ovoj retrospektivnoj studiji sudjelovali su bolesnici s dijagnozom sistemskog vaskulitisa i vaskulitisa ograničenog na kožu liječenih u Zavodu za reumatologiju, kliničku imunologiju i alergologiju Kliničkoga bolničkog centra Osijek u razdoblju od 30 mjeseci (od studenog 2016. do lipnja 2019. godine). Klinički podatci prikupljeni su pretraživanjem medicinske dokumentacije. *Rezultati:* U studiju je uključeno ukupno 46 bolesnika, 30 s dijagnozom sistemskog vaskulitisa i 16 s vaskulitisom ograničenim na kožu. Među dvjema skupinama bilo je statistički značajne razlike po spolu (sistemski vaskulitis vs vaskulitis ograničen na kožu – ženski spol 76,67% vs 43,75%; p=0,026), no među grupama nije bilo razlike u dobi pojave bolesti. Tromboembolijski događaji bili su češći u bolesnika sa sistemskim oblikom vaskulitisa (p=0,0321). Pri analizi bolesnika sa sistemskim vaskulitisom kao rizični čimbenici za razvoj TE događaja utvrđeni su zahvaćanje više organskih sustava bolešću te mlađa životna dob. *Zaključak:* U našem istraživanju pokazali smo da bolesnici sa sistemskim vaskulitisom, mlađe životne dobi, uz visoku aktivnost bolesti i zahvaćanje više organskih sustava imaju povećan rizik za nastanak tromoebolijskih događaja te bi se kod takvih bolesnika trebala posvetiti posebna pozornost u otkrivanju dodatnih rizičnih čimbenika kao što je genetska predispozicija u svrhu sprječavanja neželjenih događaja te primjenu pravovremene TE profilakse.

Ključne riječi: sistemski vaskulitis, vaskulitis ograničen na kožu, tromboembolija

Abstract

Objectives: Vasculitis is a rare disease characterized by inflammation and necrosis of blood vessels. Inflammation-induced thrombosis is a hallmark of several autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome (SS), and systemic vasculitis. In this study, we aimed to investigate the frequency of thromboembolic (TE) events in the systemic form of vasculitis and cutaneous vasculitis and to determine

the possible risk factors for developing thromboembolic events. *Methods:* In this single-centre retrospective study, the patients diagnosed with systemic vasculitis and cutaneous leukocytoclastic vasculitis were included. Medical records of the patients that were treated at the Division of Rheumatology, Clinical Immunology, and Allergology University Hospital Centre Osijek in the period of 30 months (from November 2016. to June 2019.) were analysed. *Results:* Out of a total of 46 patients who were included in the study, 30 were diagnosed with systemic vasculitis, and 16 with cutaneous vasculitis. Statistically significant differences in relation to gender were found between the two groups (systemic vasculitis vs cutaneous vasculitis: the female gender 76.67% vs 43.75%; p=0.026), but there was no difference between the groups in relation to the age of disease onset. Thromboembolic events were found to be more frequent in the systemic form of the disease (p=0.0321). In the systemic vasculitis group, TE events were found in patients who suffered from involvement of multiple organ systems and in younger patients. *Conclusion:* Our research found that patients with systemic vasculitis, who are younger, with high disease activity, and who suffered from the involvement of multiple organ system, have an increased risk for developing TE events. In those patients, special attention should be paid to searching for additional TE risk factors, such as genetics, for the purpose of preventing unwanted events and applying TE prophylaxis on time.

Keywords: Systemic vasculitis, cutaneous leukocytoclastic vasculitis, thromboembolism

INTRODUCTION

Vasculitis is a rare disease characterized by inflammation and necrosis of blood vessels. Inflammation-induced thrombosis is a hallmark of several autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome (SS), and systemic vasculitis (2,3). The incidence of thromboembolic (TE) events is an important clinical manifestation of systemic vasculitis. The reason for this incidence is due to the pathomechanism of the disease and it is also related to the pathogenesis of thrombosis (2–6).

Previous research has led to gaining new insights about the prothrombotic effect of systemic inflammation in vasculitis. In the pathophysiology of thrombosis in Behçet's syndrome (BS), a generalized disorder of CD4+ lymphocytes, monocytes, neutrophils is observed, as well as an increased production of pro-inflammatory cytokines such as interferon gamma (IFN-γ), tumour necrosis factor alpha, TNF-α), interleukin-1 (IL-1), IL-6, IL-8, IL-12 which causes the occurrence of the prothrombotic state (2). The incidence of TE events in vasculitis associated with antineutrophil cytoplasmic autoantibodies (ANCA) and large-vessel vasculitis has been confirmed (1,2). The highest frequency of ANCA-associated vasculitis occurs in eosinophilic granulomatosis with polyangiitis (EGPA) (1, 7, 8). One of the possible reasons is the role of eosinophils in the release of major basic protein as well as eosinophil cationic protein, which inhibit natural anticoagulant activity and activate platelets, leading to increased thrombin generation (1, 2). Endothelial dysfunction is also a characteristic of ANCA-associated vasculitis and is most likely caused by the interaction between neutrophils (activated by TNF-α and ANCA antibodies) and endothelial cells, with consequent massive oxidative stress leading to atherothrombotic complications (1, 2, 8–11).

In large-vessel vasculitis, anti-endothelial cell antibodies play a possible role in endothelial damage

UVOD

Vaskulitis je rijetka bolest karakterizirana upalom i nekrozom krvnih žila (1). Upalom inducirana tromboza smatra se svojstvom nekoliko autoimunih bolesti, poput sistemskog eritemskog lupusa (SLE), reumatoidnog artritisa (RA), Sjögrenova sindroma (SS), ali i sistemskih vaskulitisa (2,3). Pojavnost tromboemobolijskih (TE) događaja bitna je klinička manifestacija sistemskih vaskulitisa, što leži u patomehanizmu nastanka same bolesti, a povezana je i s patogenezom tromboze (2–6).

Dosadašnja istraživanja dovela su do spoznaja o protrombotskom učinku koji ima sustavna upala u vaskulitisima. U patofiziologiji tromboze u Behçetovu sindromu (BS) zamijećen je generalizirani poremećaj CD4+ limfocita, monocita, neutrofila i prekomjerna proizvodnja proupalnih citokina kao što su interferon gama (IFN-γ), čimbenika tumorske nekroze alfa (engl. *tumor necrosis factor alpha*, skr. TNF-α), interleukina (IL) 1, IL-6, IL-8, IL-12 što dovode do protrombotskog stanja (2). Potvrđena je pojavnost TE događaja u vaskulitisu povezanim s antineutrofilnim citoplazmatskim autoantitijelima (ANCA) i vaskulitisu velikih krvnih žila (1,2). Među ANCA-vaskulitisima najveća učestalost je u eozinofilnoj granulomatozi s poliangiitisom (EGPA) (1,7,8). Jedan od mogućih razloga jest uloga eozinofila u oslobađanju glavnoga bazičnog proteina kao i eozinofilnoga kationskog proteina koji inhibiraju prirodnu antikoagulantnu aktivnost i aktiviraju trombocite, dovodeći do prekomjernog stvaranja trombina (1,2). Disfunkcija endotelnih stanica također je svojstvo ANCA-vaskulitisa i najvjerojatnije je uzrokovana interakcijom između neutrofila (aktiviranih TNF-α i ANCA-protutijelima) i endotelnih stanica, s posljedičnim masivnim oksidativnim stresom što vodi prema aterotrombotskim komplikacijama (1,2,8–11).

Kod vaskulitisa velikih krvnih žila moguću ulogu u oštećenju endotela imaju antiendotelna protutijela

(12,13). One of the possible vascular complications is the development of aneurysms as a consequence of inflammatory damage (12, 13). Reshaping of the blood vessel wall begins in the adventitia with an infiltrate consisting mainly of auxiliary lymphocytes (T-helper cells, Th) Th1 /Th17 that activate residual dendritic cells and macrophages, which produce pro-inflammatory cytokines and growth factor that causes intimal hyperplasia (12, 13, 14, 15). The objective of this paper was to compare the incidence of TE events in systemic vasculitis and localized cutaneous vasculitis and to determine the possible risk factors for the development of TE events on a sample of patients in a tertiary care rheumatology centre.

SUBJECTS AND METHODS

In this research, a retrospective, systematic analysis and comparison of two groups of patients diagnosed with systemic vasculitis and cutaneous vasculitis are carried out, in order to determine the incidence of TE events in each group. The inclusion criterion for the study was the diagnosis of primary vasculitis according to the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasulitides (16) set by a rheumatologist/immunologist, and the exclusion criterion was the occurrence of another inflammatory rheumatic disease, malignant disease or proven infection at the time of diagnosis. 46 patients with diagnosed systemic vasculitis and cutaneous vasculitis, who were treated at the University Hospital Centre Osijek during a period of 30 months (from November 2016 to June 2019) were included in the study. Retrograde assessment was used to determine disease activity in patients with systemic vasculitis by using medical records according to the Birmingham Vasculitis Activity Score (BVAS). Data from the patient's medical history and clinical status at the time of diagnosis were analysed in relation to the incidence and type of cutaneous manifestations and manifestations on visible mucous membranes, muscle involvement, symptoms related to the respiratory and cardiovascular systems, neurological symptoms and symptoms of gastrointestinal system involvement, as well as laboratory findings (including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), detection of nitrogen-containing metabolites, etc.) in addition to various imaging methods that were performed depending on the symptoms (e.g. echocardiogram, multislice computed tomography (MSCT) of the thorax and abdomen, positron emission tomography / computed tomography (PET/CT), electromyography, etc.). The data were collected from the available medical documentation of the Division of Rheumatology, Clinical Immunology and Allergology at the University Hospital Centre Osijek (outpatient clinics, day hospitals and inpatient facilities). The research was conducted in accordance

(12,13). Jedna od mogućih vaskularnih komplikacija jest razvoj aneurizmi kao posljednice upalnog oštećenja (12,13). Preoblikovanje zida krvne žile započinje u adventiciji s infiltratom koji se uglavnom sastoji od pomoćničkih limfocita (engl. *T-helpper*, skr. Th) Th1/Th17 koji aktiviraju rezidualne dendritičke stanice i makrofage, a koji proizvode proupalne citokine i čimbenik rasta koji uzrokuje hiperplaziju intime (12–15). Cilj ovog rada bio je usporediti pojavnost TE događaja u sistemskom obliku vaskulitisa i u lokaliziranom kožnom vaskulitisu te utvrditi moguće rizične čimbenike za razvoj TE događaja u uzorku bolesnika jednoga tercijarnog reumatološkog centra.

ISPITANICI I METODE

U ovom istraživanju radi se retrospektivnoj, sistematskoj analizi i usporedbi dviju skupina bolesnika s dijagnozom sistemskog vaskulitisa i vaskulitisa ograničenog na kožu, u svrhu utvrđivanja pojavnosti TE događaja u pojedinoj skupini. Uključni kriterij za istraživanje bila je dijagnoza primarnog vaskulitisa sukladno Međunarodnom Chapel Hill konsenzusu iz 2012. godine (engl. *2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides*) (16), postavljena od strane reumatologa/imunologa, a isključni kriterij bila je prisutnost druge upalne reumatske bolesti, zloćudne bolesti ili dokazane infekcije u trenutku dijagnoze. U studiju je uključeno 46 bolesnika s dijagnosticiranim sistemskim vaskulitisom i vaskulitisom ograničenim na kožu liječenih u KBC-u Osijek u razdoblju od 30 mjeseci (od studenog 2016. do lipnja 2019. godine). Aktivnost bolesti u pacijenata sa sistemskim vaskulitisom procijenjena je retrogradno koristeći se medicinskom dokumentacijom prema skali *Birmingham Vasculitis Activity Score* (BVAS). Analizirani su podatci iz anamneze i kliničkog statusa pacijenta u trenutku dijagnoze o pojavi i vrsti kožnih promjena i promjena na vidljivim sluznicama, zahvaćanju mišića, simptomima vezanim uz dišni, srčani i krvožilni sustav, neurološkim simptomima te simptomima zahvaćanja probavnog sustava, potom laboratorijski nalazi (uključujući C-reaktivni protein [CRP], sedimentaciju eritrocita [SE], nalaz dušičnih metabolita itd.) te različite slikovne metode koje su se provodile ovisno o simptomima (npr. ultrazvuk srca, višeslojna kompjutorizirana tomografija [MSCT] prsnog koša i abdomena, pozitronska emisijska tomografija i kompjutorizirana tomografija [PET CT], elektromiografija itd.). Podatci su prikupljeni iz dostupne medicinske dokumentacije Zavoda za reumatologiju, kliničku imunologiju i alergologiju Kliničkoga bolničkog centra Osijek (ambulanti, dnevne bolnice i stacionara). Istraživanje je provedeno sukladno etičkim standardima institucije i Etičkom kodeksu udruge *World Medical Association* (Helsinška deklaracija iz 1964. i njezine

with the ethical standards of the institution and with the International Code of Medical Ethics of the World Medical Association (1964 Declaration of Helsinki and its updated versions) (17) with the approval of the institution's Ethics Committee (approval no. R2-13170/2020).

In terms of statistical methods for testing the difference in distributions for two variables, the Mann-Whitney test was used. Chi-squared test and Fisher's exact test were used to test the dependence between two categorical variables. The threshold value for the significance of the difference was set at $p<0.05$.

RESULTS

Out of a total of 46 patients, 30 were diagnosed with systemic vasculitis, and 16 with cutaneous vasculitis. Statistically significant differences in relation to gender were found between the two groups (systemic vasculitis vs cutaneous vasculitis: the female gender 76.67% vs 43.75%; p=0.026), but there was no difference between the groups in relation to the age of disease onset. A total of 5 TE events were recorded, 2 of which were a case of deep vein thrombosis, 1 was a case of arterial thrombosis, 1 was a case of pulmonary embolism and 1 was a case of cerebrovascular insult. TE events occurred more often in patients with systemic vasculitis (16.67% vs 0%; p=0.032). (Table 1). When analysing patients with systemic vasculitis, it became apparent that TE events occurred in those who suffered from the involvement of multiple organ systems (4 vs 3; p=0.0425) and in those patients who were younger (47 vs 65 years of age, p=0.018). No difference was found in relation to BVAS in the two groups of patients (19 vs 12, p=0.169) (Table 2). Distribution of patients by gender, age and occurrence of thromboembolic events (TE) according to the basic diagnosis is presented in Table 3. All patients who experienced a TE event were diagnosed with hereditary thrombophilia, which is defined by the lack of antithrombin, protein C, protein S, and mutation of factor V Leiden and prothrombin variants.

DISCUSSION

In our research, we analysed patients with systemic vasculitis and cutaneous vasculitis. Between the two groups, the incidence of TE events was exclusively characteristic of patients with systemic vasculitis.

According to the data published so far in the literature, when it comes to vasculitis, the incidence of TE events in Behçet's syndrome is the most frequently researched topic, in addition to the incidence of venous thromboembolism and arterial thrombosis (2, 18–20). According to our results, in accordance with previous knowledge, in one patient, who is also the only one diagnosed with Behçet's syndrome during that period, a TE event was determined as the outcome of an active disease.

In their retrospective cohort study, Kang et al. studied the incidence of TE events in patients with ANCA-

kasnije inačice) (17), uz odobrenje Etičkog povjerenstva institucije (br odobrenja R2-13170/2020.).

Od statističkih metoda za testiranje razlike u distribucijama za dvije varijable upotrijebljen je Mann-Whitneyev test. Za testiranje zavisnosti između dvije kategorijalne varijable upotrijebljen je Chi-2 test i Fisherov egzaktni test. Granična vrijednost za značajnost razlike je utvrđena na $p<0,05$.

REZULTATI

Od ukupno 46 bolesnika, 30 je imalo dijagnozu sistemskog vaskulitisa, a 16 vaskulitisa ograničenog na kožu. Među dvjema skupinama nađena je statistički značajna razlika po spolu (sistemski vaskulitis vs vaskulitis ograničen na kožu – ženski spol 76,67% vs 43,75%; p=0,026), no među grupama nije bilo razlike u dobi pojave bolesti. Zabilježeno je ukupno pet TE događaja, od kojih su dvije duboke venske tromboze, jedna arterijska tromboza, jedna plućna tromboemobolija i jedan cerebrovaskularni inzult. TE događaji su se češće javljali u bolesnika sa sistemskim oblikom (16,67% vs 0%; p=0,032) (tablica 1). Pri analizi bolesnika sa sistemskim vaskulitisom, TE događaji su se pojavili u onih koji su imali više zahvaćenih sustava (4 vs 3; p=0,0425) te u onih bolesnika koji su mlađe dobi (47 vs 65 godina, p=0,018). Nije nađena razlika u odnosu na BVAS u dvije skupine bolesnika (19 vs 12, p=0,169) (tablica 2). Raspodjela bolesnika po spolu i dobi i pojavnosti tromboembolijskih događaja (TE) s obzirom na osnovnu dijagnozu prikazana je u tablici 3. U svih bolesnika s TE događajem utvrđena je hereditarna trombofilija koja je definirana nedostatkom antitrombina, proteina C, proteina S te mutacijom faktora V Leiden i protrombinskih varijanti.

RASPRAVA

U našem istraživanju analizirali smo bolesnike sa sistemskim vaskulitisom i vaskulitisom ograničenim na kožu. Između dvije grupe, pojava TE događaja bila je isključivo obilježje bolesnika sa sistemskim oblikom vaskulitisa.

Prema do sada objavljenim podatcima iz literature među vaskulitisima najistraženija je pojava TE događaja u Behçetovu sindromu, uz pojavu i venskih i arterijskih tromboza (2,18–20). U našim je rezultatima, sukladno dosadašnjim spoznajama, kod jedne bolesnice, koja je ujedno i jedina kojoj je u tom razdoblju postavljena dijagnoza Behçetova sindroma, kao ishod aktivne bolesti utvrđen TE događaj.

U svojoj retrospektivnoj kohortnoj studiji Kang i suradnici proučavali su incidenciju TE događaja u bolesnika s ANCA-vaskulitisima i dokazali povećanu incidenciju TE incidenata u odnosu na opću populaciju Velike Britanije, posebno u prvoj godini dijagnoze, što

Table 1 Comparison of the main features of interest to a group of patients with systemic vasculitis and cutaneous vaculitis
Tablica 1. Usporedba glavnih obilježja od interesa skupine bolesnika sa sistemskim vaskulitisom i vaskulitisom ograničenim na kožu

		Thromboembolic events in patients with vasculitis / TE događaj u bolesnika sa vaskulitisom		P*
		Cutaneous vasculitis / Vasulitis ograničen na kožu (N=16)	Systemic vasculitis / Sistemski vaskulitis (N=30)	
Gender / Spol	Women / Žene	43,75%	76,67%	**0,0266**
	Men / Muškarci	56,25%	23,33%	
Age (Median, Interquartile range) / Dob (medijan, interkvartilni raspon IQR)		59 (±16)	62 (±14)	0,7643
Thromboembolic event / TE	Yes / Da	0%	16,67%	**0,0321**
	No / Ne	100%	83,33%	

P < 0.05

Table 2 Features of patients with Systemic Vasculitis
Tablica 2. Osobitosti bolesnika sa sistemskim vaskulitisom

		Thromboembolic event / TE događaj (N=5)	Without thromboembolic event / Bez TE događaja (N=25)	P*
Gender / Spol	Woman / Žene	80%	76%	0,6711
	Men / Muškarci	20%	24%	
Age (Median, lQR) / Dob (medijan, IQR)		47 (±15)	65 (±15)	**0,0189**
Median (IQR) / BVAS (medijan, lQR)		19 (11)	12 (11)	0,1694

P < 0.05; BVAS – Birmingham Vasculitis Activity Score

Table 3 Distribution of patients by gender, age and occurrence of thromboembolic events (TE) according to the basic diagnosis
Tablica 3. Raspodjela bolesnika po spolu i dobi i pojavnosti tromboembolijskih događaja (TE) s obzirom na osnovnu dijagnozu

	IgA vasculitis / IgA vaskulitis	GPA	EGPA	GCA	MPA	Bechet's disease / Behcetova bolest	In total / Ukupno
Men / Muškarci	3	4	0	0	0	0	7
Woman / Žene	1	8	6	3	4	1	23
In total / Ukupno	4	12	6	3	4	1	30
TE	1	1	2	/	/	1	5

GPA – granulomatosis with polyangiitis / granulomatoza s poliangiitisom; EGPA – eosinophilic granulomatosis with polyangiitis / eozinoflina granulomatoza s poliangiitisom; GCA – giant cell arteritis / gigantoceulularni arteritis; MPA – microscopic polyangiitis / mikroskopski poliangitis

associated vasculitis and demonstrated an increased incidence of TE events in comparison to the reported rates of the general population of UK, especially in the first year of diagnosis, which they associate with disease activity or with treatment (21). In our research, TE events occurred in those patients who suffered from multiple organ systems involvement and in patients who were younger. Similar observations were published by Salmela et al. in their observational study in which they demonstrated increased D-dimer values during active disease in ANCA-associated vasculitis, and in correlation with BVAS, they suggested that activation of coagulation is associated with ANCA-associ-

povezuju s aktivnošću bolesti ili s liječenjem (21). U našem istraživanju TE događaji pojavili su se u onih bolesnika koji su imali više zahvaćenih sustava te u onih bolesnika koji su mlađe dobi. Slična zapažanja objavili su Salmela i suradnici u svojoj opservacijskoj studiji u kojoj su dokazali povišene vrijednosti D-dimera tijekom aktivne bolesti u ANCA-vaskulitisu, a u korelaciji s BVAS-om sugerirali su da je aktiviranje koagulacije povezano s ANCA-vaskulitisom koji zahvaća više organskih sustava (22). Studija iz Nizozemske izvijestila je o incidenciji venskih TE incidenata od 1,8 na 100 osoba godišnje, povećavajući se na 6,7 po 100 osoba godišnje tijekom aktivne bolesti koja je defi-

ated vasculitis which involves multiple organ systems (22). A similar study from the Netherlands reported an incidence of venous TE events of 1.8 per 100 person-years, increasing to 6.7 per 100 person-years during active disease, which was characterized by a time interval of two months before and after diagnosis, or relapse in patients with ANCA-associated vasculitis, excluding eosinophilic granulomatosis with polyangiitis (EGPA) (3). The data from that study confirm that active disease is a risk factor for the incidence of TE events (3). According to a study conducted in 2007 by Stassen et al., they found that the risk of developing venous TE events in ANCA-associated vasculitis is increased, especially in active disease, which they associated with endothelial dysfunction and hypercoagulability (5). The results of the 2017 Kronbichler report highlight the role of C-reactive protein, baseline creatinine, cutaneous and gastrointestinal involvement in risk stratification associated with thromboembolic events (23).

In a 2016 meta-analysis, Ungprasert and Koster showed a significantly increased risk of venous TE events in patients suffering from granulomatosis with polyangiitis (GPA), polyarteritis nodosa (PAN) and giant cell arteritis (GCA) (6). They also showed that the frequency of hereditary thrombophilia is not increased in patients with GPA and GCA and that it is not a risk factor in the incidence of TE (6). In our study, genetic diagnosis of hereditary thrombophilia was not performed routinely in all patients, but only in patients with a proven TE event. Given that the results of our research showed an increased TE event in patients with high disease activity, hereditary haemophilia was an additional factor that contributed to the development of thrombosis in patients with a more severe clinical features with involvement of multiple organ systems.

Hereditary thrombophilia is a known factor in the incidence of venous thromboembolism in the general population (24, 25, 26). In their research, Sebastian et al. proved that the prevalence of cardiolipin antibodies as a prothrombin gene mutation (PGM) and methylenetetrahydrofolate reductase mutation (MTHFR) is not higher in patients with GPA in comparison to the general population, and they proved that the increased risk of TE events is not explained by the increased prevalence of anticardiolipin antibodies (aCL), anti-beta-2-glycoproteins or PGM and MTHFR mutations (26). In their paper, Espinosa et al. proved that patients with GCA have a high prevalence of antiphospholipid antibodies (aPL) which is not related to ischemic manifestations and that ischemic manifestations in GCA patients are not related to congenital thrombophilic risk factors (27).

The ageing process in humans is accompanied by changes in the coagulation system and thereby the risk of thrombosis is increased in older people (24). Concentrations of coagulation factors such as factor V, factor

nirana vremenskim intervalom dva mjeseca prije i nakon dijagnoze, ili recidiva u bolesnika s ANCA-vaskulitisom, a isključujući eozinofilnu granulomatozu s poliangitisiom (engl. *eosinophilic granulomatosis with polyangiitis* – EGPA) (3). Podatci te studije potvrđuju da je aktivna bolest rizični čimbenik za nastanak TE događaja (3). Stassen i suradnici u studiji iz 2007. godine otkrili su da je povećan rizik razvoja venskih TE događaja u ANCA-vaskulitisu, posebice u aktivnoj bolesti, što su povezali s endotelnom disfunkcijom i hipekoagulabilnošću (5). Rezultati izvješća Kronbichlera iz 2017. godine ističu ulogu C-reaktivnog proteina, početnog kreatinina, uključenosti kože i probavnog sustava u stratifikaciji rizika povezanih s trombembolijskim događajima (23).

U metaanalizi iz 2016. godine Ungprasert i Koster prikazali su značajno povišen rizik venskih TE događaja u pacijenata koji boluju od granulomatoze s poliangitisom (engl. *granulomatosis with polyangiitis* – GPA), nodoznog poliarteritisa (engl. *polyarteritis nodosa* – PAN) i gigantocelularnog arteritisa (engl. *giant cell arteritis* – GCA) (6). Prikazali su također da učestalost nasljedne trombofilije nije povećana u pacijenata s GPA i GCA te nije rizični čimbenik u nastanku TE (6). U našem istraživanju genetska dijagnostika hereditarne trombofilije nije rađena rutinski u svih pacijenata, već samo u onih kod kojih je dokazan TE događaj. S obzirom na to da su rezultati našeg istraživanja prikazali povećan TE događaj u pacijenata s visokom aktivnosti bolesti, nasljedna hemofilija bila je dodatni čimbenik koji je kod bolesnika s težom kliničkom slikom uz zahvaćanje više organskih sustava pridonio razvoju tromboze.

Hereditarna trombofilija je inače poznati čimbenik nastanka venskih tromboembolija u općoj populaciji (24,25,26). Sebastian i suradnici u svojem su istraživanju dokazali da prevalencija kardiolipinskih protutijela kao mutacija protrombinskog gena (engl. *prothrombin gene mutation* – PGM) i mutacija metilenhidrofolat reduktaze (engl. *methylenetetrahydrofolate reductase* – MTHFR) nije veća u pacijenata s GPA nego u općoj populaciji, te su dokazali da povećan rizik TE događaja nije objašnjen povećanom prevalencijom antikardiolipinskih protutijela (engl. *anti-cardiolipin antibody* – aCL), anti-beta2 glikoproteinom ili mutacijama PGM i MTHFR (26). Espinosa i suradnici u svojem su radu dokazali da pacijenti s GCA imaju visoku prevalenciju antifosfolipidnih proutijela (aPL) koja nije povezana s ishemijskim manifestacijama; također, ishemijske manifestacije u pacijenata s GCA nisu povezane ni s urođenim trombofilnim čimbenicima rizika (27).

Proces starenja kod ljudi popraćen je preinakama u sustavu zgrušavanja i time povećava rizik od tromboze u starijih ljudi (24). Koncentracije faktora koagulacije kao što su faktor V, faktor VII, faktor VII, faktor IX i

VII, factor VII, factor IX and fibrinogen gradually increase with age (24, 28). In our study, thromboembolic events occurred in younger patients, and a possible explanation for this lies in the increased activity of the disease and involvement of multiple organ systems in younger patients in comparison to the older population.

In our study, not a single thromboembolic event was recorded in patients with cutaneous vasculitis. By researching the available literature, no study was found that would compare the incidence of thromboembolic events in patients with cutaneous vasculitis. To our knowledge, we are the first to report an increased risk of thromboembolic events in systemic vasculitides compared to cutaneous vasculitides, so we were unable to compare our results to results from other studies.

The limitation of this research study is the small sample of subjects, considering that it is a study of a disease with a low incidence conducted in one hospital centre. Therefore, it would be preferable to expand it in the future by including more centres in the study. In addition to that, another limitation of this study is that it is a retrospective study. Also, considering that the genetic diagnosis of hereditary thrombophilia was performed only in patients with a proven TE event, so in future trials it would be necessary to determine the frequency of hereditary thrombophilia in all subjects.

CONCLUSION

Our research shows that younger patients with systemic vasculitis, high disease activity and involvement of multiple organ systems have an increased risk of thromboembolic events. The results of our research may have several clinical implications for the treatment of systemic vasculitis, and the most important objective of this research is to increase awareness of the risks for TE development. In addition to that, the objective is to propagate the performance of additional clinical trials in order to determine the need for the introduction of prophylactic anticoagulant and/or antiplatelet therapy for the prevention of TE event development.

Conflict of interest statement: The authors declare no conflict of interest

fibrinogen povećavaju se postupno s godinama (24,28). U našem istraživanju tromboembolijski događaji pojavili su se u bolesnika koji su mlađe životne dobi, a moguće objašnjenje leži u većoj aktivnosti bolesti i zahvaćenosti više organskih sustava u mlađih pacijenata u odnosu na stariju populaciju.

U našem istraživanju u bolesnika s vaskulitisom ograničenim na kožu nije zabilježen niti jedan tromboembolijski incident. Pretraživanjem dosadašnje literature nije nađeno istraživanje koje bi usporedilo pojavnost tromboembolijskih incidenata bolesnika s vaskulitisima ograničenim na kožu. Prema našim saznanjima, prvi smo koji smo prijavili povećan rizik tromboembolijskih incidenata u sistemskim vaskulitisima u odnosu na vaskulitise ograničene na kožu, stoga nismo uspjeli usporediti naše rezultate.

Ograničenje ovog istraživanja jest mali uzorak ispitanika, budući da se radi o istraživanju bolesti s malom incidencijom provedenom u jednom centru; bilo bi poželjno proširiti ga uključivanjem više centara u istraživanje. Osim toga, ograničenje studije je i retrospektivno istraživanje. Također, s obzirom na to da je genetska dijagnostika hereditarne trombofilije rađena samo kod pacijenata s dokazanim TE događajem, u budućim ispitivanjima bilo bi potrebno utvrditi učestalost hereditarne trombofilije među svim ispitanicima.

ZAKLJUČAK

Naše istraživanje pokazuje da bolesnici sa sistemskim vaskulitisom mlađe životne dobi uz visoku aktivnost bolesti i zahvaćanje više organskih sustava imaju povećan rizik za nastanak tromboebolijskih događaja. Rezultati našeg istraživanja mogu imati nekoliko kliničkih implikacija za liječenje sistemskih vaskulitisa, a najvažniji cilj ovog istraživanja jest povećati svijest o rizicima za TE, te potaknuti dodatne kliničke studije kako bi se utvrdila potreba profilaktičkog uvođenja antikoagulantne i/ili antiagregacijske terapije u svrhu sprječavanja razvoja TE događaja.

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