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ASSOCIATION BETWEEN CUTANEOUS MANIFESTATIONS AND CLINICAL FEATURES OF IgA VASCULITIS

POVEZANOST KOŽNIH MANIFESTACIJA I KLINIČKIH ZNAČAJKI IgA VASKULITISA

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Abstract

Introduction: IgA vasculitis (IgAV) is the most common systemic vasculitis in childhood. Purpuric rash is a mandatory criterion for diagnosing IgAV, it is mostly localized on the lower extremities and gluteal region, although it can also appear atypically affecting the face, trunk and upper extremities. In the most severe cases, ulcerations, necrosis and bullae can be present. *Objectives:* To evaluate the characteristics of cutaneous manifestations in patients with IgAV and to examine its association with clinical features. *Subjects and methods:* Retrospective analysis of data from patients with IgAV diagnosed and treated at the Referral Centre for Paediatric and Adolescent Rheumatology of the Ministry of Health of the Republic of Croatia, in the period from January 2009 to December 2021. *Results:* IgAV was diagnosed in 234 patients, 124 boys and 110 girls with the median (range) age at the time of diagnosis of 6.5 (4.5–8.2) years. All patients had a purpuric rash, and in 127 of them (54.3%) IgAV began with a rash. Cutaneous manifestations were most often presented in the form of palpable purpura and/or petechiae (87.2%) and in all patients were localized on the lower extremities. In 103 patients (44%) purpuric rash spread further to the upper extremities, trunk and/or face. At least one skin relapse occurred in 47 patients (20.1%). The most severe cutaneous manifestations which included ulcerations and necrosis developed in 11 patients (4.7%). Patients with cutaneous manifestations spread above the waist had a more statistically significant gastrointestinal involvement compared to patients with cutaneous manifestations affecting the lower extremities and gluteal region (50.5% vs. 36.6%, p=0.033), higher incidence of IgA vasculitis nephritis (IgAVN) (31.1% vs. 19.8%, p=0.048) and were more frequently treated with systemic glucocorticoids (68% vs. 52.7%, p=0.018) and angiotensin-converting enzyme inhibitors (14.5% vs. 5.3%, p=0.016). Almost all patients with ulcerations and necrosis required treatment with systemic glucocorticoids compared to the rest (90.9% vs. 57.8%,p=0.031). *Conclusion:* We observed that patients with purpuric rash spread above the waist have more frequently affected gastrointestinal system and a higher incidence of IgAVN. The prevalence of ulcerations and necrosis in IgAV is less common than the standard purpuric rash and this group of patients required systemic glucocorticoid therapy.

Key words: IgA vasculitis, cutaneous manifestations, children

Sažetak

Uvod: IgA vaskulitis (IgAV) najčešći je sistemski vaskulitis dječje dobi. Purpurični osip ključan je kriterij za dijagnozu IgAV-a, a najčešće je rasprostranjen po donjim udovima i gluteusima, iako može biti proširen i na atipičnim mjestima poput lica, trupa i gornjih udova. U najtežim slučajevima mogu biti prisutne ulceracije, nekroze i bule. *Cilj:* Utvrditi osobitosti kožnih promjena u bolesnika s IgAV-om te ispitati njihovu povezanost s kliničkim značajkama. *Ispitanici i metode:* Retrospektivna analiza podataka bolesnika s IgAV-om dijagnosticiranih i liječenih u Referentnom centru za pedijatrijsku i adolescentnu reumatologiju Ministarstva zdravstva RH, u razdoblju od siječnja 2009. do prosinca 2021. godine. *Rezultati:* IgAV je dijagnosticiran u 234 bolesnika, 124 dječaka i 110 djevojčica s medijanom (rasponom) dobi u trenutku dijagnoze 6,5 (4,5 – 8,2) godina. Svi su bolesnici imali kožni osip, a u njih 127 (54,3%) IgAV je i započeo osipom. Kožne promjene najčešće su bile zastupljene u obliku palpabilne purpure i/ili petehija (87,2%) i u svih bolesnika bile su lokalizirane po donjim udovima. U 103 bolesnika (44%) kožni osip se dalje proširio na ruke, trup i/ili lice. U 47 bolesnika (20,1%) došlo je do barem jednog recidiva kožnih promjena. Najteže kožne promjene u vidu ulceracija i nekroza razvilo je 11 bolesnika (4,7%). Bolesnici s kožnim promjenama proširenim iznad donjih udova imali su statistički značajno češće zahvaćen gastrointestinalni sustav u odnosu na bolesnike s kožnim osipom ograničenim na donje udove i glutealno (50,5% u odnosu na 36,6%, p=0,033), veću pojavnost nefritisa (IgAVN) (31,1% u odnosu na 19,8%, p=0,048) te su češće liječeni sistemskim glukokortikoidima (68% u odnosu na 52,7%, p=0,018) i inhibitorima angiotenzin konvertaze (14,5% u odnosu na 5,3%, p=0,016). Gotovi svi bolesnici s ulceracijama i nekrozama zahtjevali su liječenje sistemskim glukokortikoidima u odnosu na sve preostale bolesnike (90,9% u odnosu na 57,8%, p=0,031). *Zaključak:* Uočili smo da bolesnici s kožnim osipom proširenim iznad donjih udova imaju češće zahvaćen gastrointestinalni sustav i češću pojavu IgAVN-a. Učestalost ulceracija i nekroza u IgAV-u rjeđa je od klasične slike kožnog osipa i takvi bolesnici zahtijevali su liječenje sistemskim glukokortikoidima.

Ključne riječi: IgA vaskulitis, kožne manifestacije, djeca

INTRODUCTION

IgA vasculitis (IgAV), formerly known as Henoch-Schönlein purpura (HSP), is the most common form of childhood vasculitis with an estimated worldwide annual incidence of 3–55.9 cases per 100,000 children (1–3). In the Republic of Croatia, the average annual incidence of IgAV is 6.79 per 100,000 children (4). Palpable purpura and/or petechiae without thrombocytopenia and other underlying coagulation disorders are a recognizable feature of the disease and at the same time a necessary criterion in making a diagnosis (5). The purpuric rash is most often spread on the extensor sides of the lower extremities and the gluteal region, although it can also be spread to the upper extremities, abdomen, face and ears. In the beginning, the skin lesions appear as clusters of erythema, urticaria and maculopapular rash, and then they turn into petechiae, ecchymoses and purple induration up to 1 cm in diameter, which are distributed on the previously changed skin. The skin lesions then change colour from red and purple to brownish and fade after ten days, leaving some patients with areas of gradual hyperpigmentation (6). Less than 5% of children may develop necrosis, ulceration and bullae on the skin, while the appearance of such skin forms has been described in as many as 60% of adult patients (7). In such cases, as well as with skin lesions that are diffusely distributed, it is recommended to perform a skin biopsy to rule out other forms of vasculitis, especially ANCA-associated vasculitis (8). A skin biopsy in patients with IgAV shows leukocytoclastic vasculitis characterized by fibrinoid ne-

UVOD

IgA vaskulitis (IgAV), otprije poznat kao Henoch-Schönleinova purpura (HSP), najčešći je vaskulitis dječje dobi s procijenjenom svjetskom godišnjom incidencijom između 3 i 55,9 na 100.000 djece (1-3). U Republici Hrvatskoj prosječna godišnja incidencija IgAV-a je 6,79 na 100.000 djece (4). Palpabilna purpura i/ili petehije bez trombocitopenije i drugoga podležećeg koagulacijskog poremećaja prepoznatljivo su obilježje bolesti te ujedno i neophodan kriterij u postavljanju dijagnoze (5). Purpurični osip najčešće je rasprostranjen po ekstenzornim stranama donjih udova i gluteusima, premda može biti proširen i na gornje udove, trbuh, lice i uške. U početku se kožne lezije očituju kao grozdovi eritema, urtike i makulopapulozni osip, a potom prelaze u petehije, ekhimoze i ljubičaste induracije promjera do 1 cm koje su raspoređene između prethodno promijenjene kože. Kožne lezije potom mijenjaju boju od crvene i ljubičaste do smeđkaste boje, da bi nakon desetak dana izblijedjele ostavljajući kod pojedinih bolesnika područja postupalne hiperpigmentacije (6). U manje od 5% djece može doći i do razvitka nekroza, ulceracija i bula na koži, dok je pojava takvih kožnih oblika opisana u čak 60% odraslih bolesnika (7). U takvim slučajevima, kao i kod kožnih lezija koje su difuzno rasprostranjene, preporučeno je napraviti i biopsiju kože kako bi se isključili drugi vaskulitisi, posebno vaskulitisi povezani s ANCA-om (8). Biopsija kože u bolesnika s IgAV-om pokazuje leukocitoklastični vaskulitis koji obilježava fibrinoidna nekroza malih krvnih žila papilarnog der-

crosis of the small blood vessels of the papillary dermis (capillaries, venules and arterioles), perivascular oedema and neutrophil infiltration with neutrophil nucleus fragmentation, while direct immunofluorescence of the skin shows predominant IgA deposits and complement component C3 in the dermis. (5). And while the purpuric rash usually passes spontaneously, that is, with the application of short-term symptomatic treatment, the most severe cutaneous forms require special therapy. In addition to that, some previous studies have already shown that the prevalence of purpuric rash as well as recurrences of purpura can significantly contribute to the increased risk for the occurrence of more severe gastrointestinal forms of the disease as well as the development of IgA vasculitis nephritis (IgAVN), the most significant chronic complication of the disease (9–12). The aim of this paper is to show the cutaneous manifestations in IgAV and to determine the association of their characteristics with the clinical and laboratory features of the disease and the selection of therapy.

SUBJECTS AND METHODS

In the period from January 2009 to December 2021, a retrospective study was conducted at the Division of Clinical Immunology, Allergology and Rheumatology at the Department of Paediatrics, University Hospital Centre Zagreb, the Referral Centre for Paediatric and Adolescent Rheumatology of the Ministry of Health of the Republic of Croatia, which included patients younger than 18 years of age who are diagnosed with IgAV according to the EULAR/PRINTO/PRES criteria (5). The research was approved by the Ethics Committee of the University Hospital Centre Zagreb and the School of Medicine, University of Zagreb. Demographic, clinical and laboratory data on patients were collected from a database based on medical records. Demographic data included the patient's gender and age at the time of IgAV diagnosis, while clinical data included the duration of hospitalization expressed in days, the leading initial symptom of the disease, the presence and type of prodromal infection, isolated microbiological agents, the prevalence of purpuric rash, joint involvement, gastrointestinal, renal and urogenital system, the presence of severe cutaneous changes (ulcerations, necrosis, bullae), time from the onset of the disease to the onset of nephritis (in days), systolic blood pressure values, skin biopsy, kidney biopsy, type of medication and number of relapses. Purpuric rash is categorized into one of two groups according to its prevalence: 1. purpuric rash localized on the lower extremities and the gluteal region; 2. purpuric rash spread above the lower extremities to the upper extremities, trunk and face (generalized purpura). Disease relapse was defined as the recurrence of symptoms and signs

misa (kapilare, venule i arteriole), perivaskularni edem i neutrofilna infiltracija s fragmentacijom njihovih jezgara, dok nalaz direktne imunofluorescencije kože pokazuje predominantne IgA depozite i C3 komponente komplementa u dermisu (5). I dok purpurični osip uobičajeno prolazi spontano, odnosno na primjenu kratkotrajnoga simptomatskog liječenja, najteži kožni oblici zahtijevaju posebnu terapiju. Osim toga, već su neka prethodna istraživanja pokazala da rasprostranjenost purpuričnog osipa kao i recidivi purpure mogu značajno pridonositi povećanom riziku za nastanak težih gastrointestinalnih oblika bolesti, kao i razvitku IgA vaskulitis nefritisa (IgAVN), najznačajnije kronične komplikacije bolesti (9-12). Cilj ovog rada jest prikazati kožne manifestacije u IgAV-u te utvrditi povezanost njihovih osobitosti s kliničkim i laboratorijskim značajkama bolesti te odabir terapije.

ISPITANICI I METODE

U razdoblju od siječnja 2009. do prosinca 2021. u Zavodu za kliničku imunologiju, reumatologiju i alergologiju Klinike za pedijatriju Kliničkoga bolničkog centra Zagreb, Referentnom centru za pedijatrijsku i adolescentnu reumatologiju Ministarstva zdravstva Republike Hrvatske, provedeno je retrospektivno istraživanje u koje su uključeni bolesnici mlađi od 18 godina s postavljenom dijagnozom IgAV-a sukladno EULAR/PRINTO/PRES kriterijima (5). Istraživanje je odobrilo Etičko povjerenstvo Kliničkoga bolničkog centra Zagreb i Medicinskog fakulteta Sveučilišta u Zagrebu. Demografski, klinički i laboratorijski podatci o bolesnicima prikupljeni su iz baze podataka temeljene na medicinskoj dokumentaciji. Demografski podatci uključivali su spol i dob pri dijagnozi IgAV-a, dok su klinički podatci uključivali trajanje hospitalizacije izražene u danima, vodeći početni simptom bolesti, postojanje i vrstu prodromalne infekcije, izolirane mikrobiološke uzročnike, rasprostranjenost purpuričnog osipa, zahvaćenost zglobova, gastrointestinalnog sustava, bubrega i urogenitalnog sustava, prisutnost teških kožnih promjena (ulceracije, nekroze, bule), vrijeme od početka bolesti do pojave nefritisa (u danima), vrijednosti sistoličkoga krvnog tlaka, biopsiju kože, biopsiju bubrega, vrstu lijekova i broj relapsa. Purpurični je osip prema rasprostranjenosti kategoriziran u jednu od dvije skupine: 1. purpurični osip lokaliziran na donjim udovima i glutealno; 2. purpurični osip proširen iznad donjih udova na gornje udove, trup i lice (generalizirana purpura). Relaps bolesti definiran je kao ponovna pojava simptoma i znakova karakterističnih za IgAV nakon asimptomatskog razdoblja u trajanju od najmanje jednog mjeseca. Laboratorijski nalazi uključivali su upalne pokazatelje: sedimentaciju eritrocita (SE), C-reaktivni protein (CRP) i feritin; broj eritrocita, hemoglobin, hematokrit, broj leukocita, broj trombocita; biokemijske pretrage krvi: kreatinin,

characteristic of IgAV after an asymptomatic period of at least one month. Laboratory findings included inflammatory indicators: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and ferritin; red blood cell count, haemoglobin, haematocrit, white blood cell count, platelet count; biochemical blood tests: creatinine, urea, estimated glomerular filtration rate (eGFR), total proteins, serum albumins; coagulation factor tests: prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, D-dimers; urine tests: presence of erythrocyturia (defined as >5 erythrocytes in urine sediment) and/or proteinuria (defined as ≥2+ proteins in urine sediment), albumin/creatinine ratio in urine (values >3 mg/mmol were considered pathological); 24-hour urine analysis for quantification of proteinuria (defined as >0.15 g/day of total excreted proteins); immunological tests: immunoglobulin classes (IgA, IgG, IgM, total IgE), antinuclear antibodies (ANA), complement components C3 and C4, total complement activity (CH50), antistreptolysin O titer (ASTO) and faecal occult blood test (FOBT). Microbiological tests performed on patients with a history of infection included a nasopharyngeal swab.

Statistical processing of the data was performed using the MedCalc program for the Windows operating system, and the data were presented in tables and graphics. The normality of data distribution was tested using the Shapiro–Wilk test. Continuous variables for values that do not have a normal distribution are shown as the median and interquartile range (25 to 75 percentiles), and categorical variables are shown as percentages. Differences in categorical variables between two groups of patients were examined using the $\chi 2$ test and Fisher's exact test, and in quantitative variables using the Mann-Whitney U test. All p-values lower than 0.05 were considered as statistically significant.

RESULTS

In the period from 1st January 2009 to 31st December 2021, 234 patients were diagnosed with IgAV, among whom there were 124 boys and 110 girls, in a ratio of 1.13:1 with a median age of 6.5 (4,5–8,2) years of age at the time of the diagnosis. Table 1 shows the demographic and clinical characteristics of patients with IgAV.

The most common skin efflorescences in the mentioned cohort of patients were papules in combination with purpuric changes, which were present in 122 patients (52.2%). The next most frequent occurrences were isolated petechiae, which were present in 82 patients (35%), while the rarest was a combination of purpuric and macular changes (in 15 patients, or 6.4%). Purpuric changes with hematomas were present in 4 patients (1.7%). 11 patients (4.7%) had severe cutaneureju, procijenjenu glomerularnu filtraciju (engl. *estimated glomerular filtration rate*, eGFR), ukupne proteine, serumske albumine; koagulacijske pretrage: protrombinsko vrijeme (PV), aktivirano parcijalno tromboplastinsko vrijeme (APTV), fibrinogen, D-dimere; pretrage urina: prisutnost eritrociturije (definirane kao >5 eritrocita u sedimentu urina) i/ili proteinurije (definirane kao ≥2+ proteina u sedimentu urina), omjer albumin/kreatinin u urinu (vrijednosti >3 mg/mmol smatrane su patološkim); analizu 24-satnog urina za kvantifikaciju proteinurije (definirane kao >0,15 g/dU sveukupno izlučenih proteina); imunološke pretrage: razrede imunoglobulina (IgA, IgG, IgM, ukupni IgE), antinuklearna antitijela (ANA), C_3 i C_4 komponente komplementa, razinu ukupnog komplementa (CH_{50}), antistreptolizinski O titar (ASTO) i analizu stolice na okultno krvarenje. Mikrobiološke pretrage u bolesnika s anamnezom infekcije uključivale su obrisak nosne sluznice i ždrijela.

Statistička obrada podataka izvršena je pomoću programa *MedCalc* za operativni sustav *Windows*, a podatci su prikazani tablično i grafički. Normalnost raspodjele podataka ispitivana je pomoću Shapiro-Wilkovljevog testa. Kontinuirane varijable za vrijednosti koje nemaju normalnu distribuciju prikazane su kao medijan i interkvartilni raspon (od 25 do 75 centile), a kategoričke varijable prikazane su u postotcima. Razlike u kategorijskim varijablama između dviju grupa pacijenata ispitivane su pomoću $\chi 2$ testa i Fisherovog egzaktnog testa, a u kvantitativnim pomoću Mann-Whitneyjevog U-testa. Sve p-vrijednosti manje od 0,05 smatrane su statistički značajnima.

REZULTATI

U razdoblju od 1. siječnja 2009. do zaključno 31. prosinca 2021. dijagnosticirano je 234 bolesnika s IgAV-om, među kojima je bilo 124 dječaka i 110 djevojčica, u omjeru 1,13:1 s medijanom dobi od 6,5 (4,5 – 8,2) godina u trenutku dijagnoze. U tablici 1 prikazane su demografske i kliničke karakteristike bolesnika s IgAV-om.

Najčešće kožne eflorescencije u navedenoj kohorti bolesnika bile su papule u kombinaciji s purpuričnim promjenama, koje su bile prisutne u 122 bolesnika (52,2%). Sljedeće su po učestalosti bile izolirane petehije, koje je imalo 82 bolesnika (35%), dok je najrjeđe bila zastupljena kombinacija purpuričnih i makuloznih promjena (u 15 bolesnika odnosno njih 6,4%). Purpuричne promjene uz hematome bile su prisutne u četiri bolesnika (1,7%). Teške kožne promjene, ulceracije i nekroze imalo je 11 bolesnika (4,7%). U 47 bolesnika (20,1%) kožne promjene imale su barem jedan recidiv. Kožni osip lokaliziran po nogama i glutealno imao je 131 bolesnik (56%), u 50 bolesnika je osip osim donjih udova zahvatio i ruke (21,4%), dok su 53 bolesnika imala za-

Table 1 Demographic and clinical features in IgAV patients, N=234
Tablica 1. Demografska i klinička obilježja bolesnika s IgAV-om, N = 234

Characteristic / Obilježje	IgAV patients with skin lesions only on the lower extremities (N=131) / IgAV bolesnici s kožnim lezijama samo po donjim ekstremitetima (N=131) N (% or/ili range/raspon)	IgAV patients with skin lesions spread above the lower extremities (N=103) / IgAV bolesnici s kožnim lezijama proširenim iznad donjih ekstremiteta (N=103) N (% or/ili range/raspon)	p-value / p vrijednost
Gender / Spol			
F / Ž	63 (48,1%)	47 (45,6%)	0,708[a]
M	68 (51,9%)	56 (54,4%)	
Age (in years) / Dob (godine)	6,5 (4,5-8,1)	6,5 (4,5-8,3)	0,7[a]
First symptom of the disease / Prvi simptom bolesti			
Skin rash / Kožni osip	67 (51,1%)	60 (58,3%)	0,278[a]
Arthritis/arthralgia / Artritis/artralgije	46 (35,1%)	26 (25,2%)	
GI system involvement / Probavni sustav	18 (13,8%)	17 (16,5%)	
Hospitalization (in days) / Hospitalizacija (dani)	10 (5-13)	12 (8-18)	**0,006**[a]
Infection / Infekcija	90 (68,7%)	67 (65%)	0,554[a]
Clinical features / Klinička slika			
Subcutaneous oedema / Subkutani edem	25 (19,1%)	18 (17,5%)	0,753[a]
Recurrent rash / Recidivirajući osip	25 (19,1%)	22 (21,4%)	0,666[a]
Severe cutaneous manifestations (ulcerations, necrosis) / Teške kožne promjene (ulceracije, nekroze)	6 (6,2%)	5 (4,8%)	0,922[b]
Skin biopsy / Biopsija kože	0 (0%)	1 (0,97%)	0,258[b]
Arthritis/arthralgia / Artritis/artralgije	102 (77,8%)	69 (67%)	0,063[a]
GI system involvement / Zahvaćanje GI sustava	48 (36,6%)	52 (50,5%)	**0,033**[a]
Severe GI complications (gastrointestinal bleeding, intussusception, intestinal invagination) / Teške GI komplikacije (krvarenje iz probavnog sustava, intususcepcija, invaginacija crijeva)	9 (6,9%)	11 (10,7%)	0,301[a]
IgAVN	26 (19,8%)	32 (31,1%)	**0,048**[a]
Time from diagnosis to onset of IgAVN: median (IQR) / Vrijeme od dijagnoze do pojave IgAVN-a: medijan (IR)	2,5 (0-5,25)	7,5 (3,25-24)	0,007[c]
Kidney biopsy / Biopsija bubrega	9 (6,8%)	16 (15,5%)	**0,033**[a]
Involvement of the scrotum and urogenital system (N= number of boys) / Zahvaćenost skrotuma i urogenitalnog sustava (N= broj dječaka)	9 (13,2%)	5 (9%)	0,573[b]
Therapy / Terapija			
NSAID	79 (60,3%)	56 (54,4%)	0,361[a]
Glucocorticoids / Glukokortikoidi	69 (52,7%)	70 (68%)	**0,018**[a]
ACE inhibitors / ACE inhibitori	7 (5,3%)	15 (14,5%)	**0,016**[a]
Immunosuppressants / Imunosupresivi	4 (3%)	8 (7,8%)	0,137[b]
Disease relapse / Relaps bolesti	25 (19,1%)	25 (24,3%)	0,336[a]

*Legend / Legenda: IgAV: IgA vasculitis / IgA vaskulitis; F/Ž: female gender / ženski spol; M: male gender / muški spol; GI: gastrointestinal / gastrointestinalni; IgAVN: IgA vasculitis nephritis / IgA vaskulitis nefritis; IQR/IR: interquartile range / interkvartilni raspon; NSAID: non-steroidal anti-inflammatory drugs / nesteroidni protuupalni lijekovi. Data are presented as percentages, statistical significance set at *P<0.05 / Podatci su prikazani u postotcima, statistička značajnost postavljena na *P<0,05. [a]X^2 test / X^2 test; [b]Fisher's exact test / Fisherov egzaktni test; [c]Mann-Whitney U-test / Mann-Whitneyjev U-test*

ous manifestations, ulcerations and necrosis. In 47 patients (20.1%), cutaneous manifestations had at least one recurrence. 131 patients (56%) had a skin rash localized on the legs and gluteal area, in 50 patients the

hvaćenu kožu nogu, ruku, trupa i lica (22,6%). Biopsija kože učinjena je u samo jednog bolesnika koji je po koži ruku i nogu imao gust purpuričan osip s eflorescencijama promjera 1 cm i centralnim nekrozama te papule po

rash affected not only the lower extremities but also the hands (21.4%), while in 53 patients the skin on the legs, arms, trunk and face was affected (22, 6%). A skin biopsy was performed on only one patient who had a dense purpuric rash on the skin of the arms and legs with efflorescences 1 cm in diameter and central necrosis and papules on the skin of the face. The skin biopsy indicated leukocytoclastic vasculitis with neutrophil infiltration, especially in the small blood vessels of the dermis and deposits of IgA and C3, and thus the histopathological finding with the clinical features of the patient was included in the diagnosis of IgAV.

A statistically significantly higher proportion of patients with skin rash spread over the lower extremities suffered from gastrointestinal system involvement (50.5% compared to 36.6%, p=0.033), they developed IgAVN (31.1% compared to 19.8%, p=0.048), they had a large amount of protein in urine (24.3% versus 12.2%, p=0.016) and underwent a kidney biopsy (15.5% versus 6.8%, p=0.033) compared to patients with a skin rash affecting the lower extremities. Patients with skin rashes spread over the lower extremities were more often treated with glucocorticoids (68% versus 52.7%, p=0.018) and antihypertensives from the group of angiotensin-converting enzyme inhibitors (14.5% versus 5.3%, p=0.016) with a longer duration of hospitalization (p=0.006), and the time to onset of IgAVN was also longer (p=0.007). No statistically significant differences between the groups were observed in laboratory findings (Table 2). Also, no statistically significant difference was observed in the involvement of the gastrointestinal system (45.5% versus 42.6%, p=0.852) and the incidence of IgAVN (45.5% versus 23.8%, p=0.146) in patients with severe cutaneous manifestations compared to the rest of the patients. Among 11 patients with severe cutaneous manifestations, 10 of them (90.9%) were treated with systemic glucocorticoids, while only one patient was treated with local glucocorticoid therapy for ulcerations. Patients with ulcerations and necrosis were statistically more significantly treated with systemic glucocorticoids compared to all other patients (90.9% vs. 57.8%, p=0.031). In 1 patient (9.1%) scars remained after ulcerations, and in 3 patients (27.3%) hyperpigmentation remained. The follow-up of all patients was performed for at least 6 months, during which time recurrences of skin rash occurred in 47 patients (20.1%). In 224 patients (95.8%) with IgAV complete recovery was achieved, while 10 of these patients (4.3%) had IgAVN with proteinuria <1 g/dU and their clinical follow-up was continued.

DISCUSSION

The purpose of this retrospective study conducted at the Referral Centre for Paediatric and Adolescent Rheumatology of the Ministry of Health of the Republ-

koži lica. Bioptat kože ukazivao je na leukocitoklastični vaskulitis s neutrofilnom infiltracijom, posebno u malim krvnim žilama dermisa i depozitima IgA i C3, te je time patohistološki nalaz s kliničkom slikom bolesnika uklopljen u dijagnozu IgAV-a.

Statistički značajno veći udio bolesnika s kožnim osipom proširenim iznad donjih udova imao je zahvaćen gastrointestinalni sustav (50,5% u odnosu na 36,6%, p=0,033), razvio je IgAVN (31,1% u odnosu na 19,8%, p=0,048), imao proteinuriju u nalazu urina (24,3% u odnosu na 12,2%, p=0,016) te bio podvrgnut biopsiji bubrega (15,5% u odnosu na 6,8%, p=0,033) u odnosu na bolesnike s kožnim osipom ograničenim samo na donje udove. Bolesnici s kožnim osipom proširenim iznad donjih udova češće su liječeni glukokortikoidima (68% u odnosu na 52,7%, p=0,018) i antihipertenzivima iz skupine inhibitora angiotenzin konvertaze (14,5% u odnosu na 5,3%, p=0,016) uz dulje trajanje hospitalizacije (p=0,006), a vrijeme do nastupa IgAVN-a također je bilo dulje (p=0,007). U laboratorijskim nalazima nisu uočene statistički značajne razlike između skupina (tablica 2). Također nije uočena statistički značajna razlika u zahvaćanju gastrointestinalnog sustava (45,5% u odnosu na 42,6%, p=0,852) i pojavnosti IgAVN-a (45,5% u odnosu na 23,8%, p=0,146) u bolesnika s teškim kožnim promjenama u odnosu na sve preostale bolesnike. Među 11 bolesnika s teškim kožnim promjenama njih 10 (90,9%) liječeno je sistemskim glukokortikoidima, dok je u samo jednog bolesnika za ulceracije primijenjena lokalna glukokortikoidna terapija. Bolesnici s ulceracijama i nekrozama su statistički značajnije liječeni sistemskom glukokortikoidnom terapijom u odnosu na sve ostale bolesnike (90,9% u odnosu na 57,8%, p=0,031). Kod jednog bolesnika (9,1%) nakon ulceracija zaostali su ožiljci, a kod troje bolesnika (27,3%) hiperpigmentacije. Svi bolesnici praćeni su u vremenskom intervalu od barem šest mjeseci, tijekom kojega su se recidivi kožnog osipa javili kod 47 bolesnika (20,1%). U 224 bolesnika (95,8%) s IgAV-om došlo je do potpunog izlječenja, dok je njih 10 (4,3%) imalo IgAVN s proteinurijom <1 g/dU te je dalje nastavljeno njihovo kliničko praćenje.

RASPRAVA

Svrha ovoga retrospektivnog istraživanja provedenog u Referentnom centru za pedijatrijsku i adolescentnu reumatologiju Ministarstva zdravstva Republike Hrvatske bila je analizirati kožne manifestacije, ključni klinički kriterij za dijagnozu ovoga najčešćeg vaskulitisa dječje dobi te ukazati na moguću povezanost osobitosti kožnih promjena s drugim kliničkim i laboratorijskim značajkama bolesti. U najvećeg broja djece s IgAV-om kožne promjene su tipične u vidu palpabilne netrombocitopenične purpure lokalizirane po donjim udovima i glutealno (5,6). U našoj kohorti od 234 bolesnika svi su imali kožni osip u predjelu donjih udova, najčešće po potko-

Table 2 Laboratory findings in IgAV patients, (N=234)
Tablica 2. Laboratorijski nalazi bolesnika s IgAV-om, (N=234)

Characteristic / Obilježje	IgAV patients with skin lesions only on the lower extremities (N=131) / IgAV bolesnici s kožnim lezijama samo po donjim ekstremitetima (N=131) N (% or/ili range/raspon)	IgAV patients with skin lesions spread above the lower extremities (N=103) / IgAV bolesnici s kožnim lezijama proširenim iznad donjih ekstremiteta (N=103) N (% or/ili range/raspon)	p-value / p vrijednost
/ ESR (mm/hr): median (IQR) SE (mm/h): medijan (IR)	17 (11-32)	17 (10.4-26.5)	0.685[c]
CRP (mg/L): median (IQR) / CRP (mg/L): medijan (IR)	6.2 (1.9-13.9)	7.5 (2.4-16.8)	0.423[c]
Erythrocytes (10^{12}/L): median (IQR) / Eritrociti (10^{12}/L): medijan (IR)	4.65 (4.41-5)	4.65 (4.43-5)	0.704[c]
Hemoglobin (g/L): Median (IQR) / Medijan (IR)	126 (118-133)	127.5 (118-133)	0.354[c]
Hematocrit: median (IQR) / Hematokrit: medijan (IR)	0.36 (0.34-0.39)	0.37 (0.35-0.39)	0.629[c]
Leukocytes (10^9/L): median (IQR) / Leukociti (10^9/L): medijan (IR)	10.1 (7.9-12.5)	10.8 (8.2-13.2)	0.442[c]
Thrombocytes (10^9/L): median (IQR) / Trombociti (10^9/L): medijan (IR)	369 (307-439)	347 (279-384.5)	**0.044**[c]
Creatinine (µmol/L): median (IQR) / Kreatinin (µmol/L): medijan (IR)	42 (31-54)	41 (32-59.5)	0.859[c]
Urea (mmol/L): median (IQR) / Ureja (mmol/L): medijan (IR)	4.1 (3.3-4.7)	4 (3.4-4.8)	0.227[c]
eGFR: median (IQR) / eGFR: medijan (IR)	128.5 (115.3-147)	129 (116.5-150)	0.979[c]
Ferritin (ng/mL): median (IQR) / Feritin (ng/mL): medijan (IR)	65.3 (43.9-102.8)	70.5 (50.9-97.9)	0.895[c]
PT: median (IQR) / PV: medijan (IR)	1.0 (0.9-1.1)	0.9 (0.8-1.1)	0.179[c]
aPTT (s): median (IQR) / APTV (s): medijan (IR)	25.8 (23.8-27.7)	25.2 (23.4-26.6)	0.545[c]
Fibrinogen (g/L): median (IQR) / Fibrinogen (g/L): medijan (IR)	3.4 (2.9-4)	3.3 (2.7-4.1)	0.606[c]
D-dimer test (µg/L): median (IQR) / D-dimeri (µg/L): medijan (IR)	2.1 (0.9-4.2)	2.5 (0.7-5.1)	0.413[c]
Erythrocyturia: n(number) / Eritrociturija: n (broj)	22 (16.8%)	22 (21.4%)	0.375[a]
Proteinuria: n (number) / Proteinurija: n (broj)	16 (12.2%)	25 (24.3%)	**0.016**[a]
Urinary albumin/creatinine ratio: median (IQR) / Omjer albumin/kreatinin u urinu: medijan (IR)	6.2 (1.4-22.3)	15.7 (3.2-52.6)	0.327[c]
Proteinuria – 24 hour urine protein test (g/day): median (IQR) / Proteinurija – 24-satna (g/dU): medijan (IR)	0.09 (0.06-0.14)	0.13 (0.07-0.27)	0.836[c]
Total protein test (g/L): median (IQR) / Ukupni proteini (g/L): medijan (IR)	70 (67-74)	69.5 (65-73)	0.243[c]
Albumin test (g/L): median (IQR) / Albumini (g/L): medijan (IR)	38.5 (35.1-41.3)	38.8 (35.9-42.4)	0.865[c]
IgA (g/L): median (IQR) / IgA (g/L): medijan (IR)	1.9 (1.4-2.6)	1.8 (1.3-2.4)	0.383[c]
IgG (g/L): median (IQR) / IgG (g/L): medijan (IR)	10.2 (8.7-12.4)	9.7 (7.7-11.7)	0.312[c]
IgM (g/L) median (IQR) / IgM (g/L): medijan (IR)	0.9 (0.7-1.2)	0.9 (0.7-1.2)	0.678[c]
Total IgE (g/L): median (IQR) / ukupni IgE (g/L): medijan (IR)	85.8 (16.4-217.5)	36.2 (24.6-79.8)	0.315[c]
ANA (+/-): n (number) / (broj)	8 (6.1%)	12 (11.6%)	0.132[a]
C_3 (g/L): median (IQR) / medijan (IR)	1.26 (1.11-1.42)	1.31 (1.12-1.41)	0.749[c]
C_4 (g/L): median (IQR) / medijan (IR)	0.26 (0.21-0.31)	0.24 (0.18-0.3)	0.502[c]
CH_{50} (%): median (IQR) / medijan (IR)	97 (85-111)	94 (79-110)	0.860[c]
ASTO: median (IQR) / medijan (IR)	161 (69-492)	155 (22-421.8)	0.161[c]
Positive faecal occult blood test (+/–): n(number) / Stolica pozitivna na okultno krvarenje (+/-): n (broj)	26 (19.8%)	26 (25.2%)	0.324[a]

*Legend / Legenda: ESR/SE: erythrocyte sedimentation rate / sedimentacija eritrocita; CRP: C-reactive protein / C-reaktivni protein; eGFR: estimated glomerular filtration rate / procijenjena glomerularna filtracija; PT/PV: prothrombin time / protrombinsko vrijeme; APTT/APTV: activated partial thromboplastin time / aktivirano parcijalno tromboplastinsko vrijeme; IgA: immunoglobulin A / imunoglobulin A; IgG: immunoglobulin G / imunoglobulin G; IgM: immunoglobulin M / imunoglobulin M; total IgE / uIgE: total immunoglobulin E / ukupni imunoglobulin E; ANA: antinuclear antibodies / antinuklearna antitijela; C_3: complement component C_3 / C_3 komponenta komplementa; C_4: complement component C_4 / C_4 komponenta komplementa; CH_{50}: total complement activity / ukupni komplement; ASTO: antistreptolysin O titer / antistreptolizinski titar; IQR/IR: interquartile range / interkvartilni raspon. Data are presented as a median (interquartile range) as well as percentages, statistical significance set at *P<0.05 / Podatci su prikazani kao medijan (interkvartilni raspon) i u postotcima, statistička značajnost postavljena na *P<0,05. [a]X^2 test / X^2 test [b]Fisher's exact test / Fisherov egzaktni test [c]Mann-Whitney U-test / Mann-Whitneyjev U-test*

lic of Croatia was to analyse the cutaneous manifestations, the key clinical criterion for the diagnosis of this most common childhood vasculitis, and to point out the possible connection between the characteristics of the cutaneous manifestations and other clinical and laboratory features of the disease. In the majority of children with IgAV, cutaneous manifestations are typical in the form of palpable non-thrombocytopenic purpura localized on the lower extremities and the gluteal region (5,6). In our cohort of 234 patients, all had a case of skin rash in the area of the lower extremities, most often on the lower extremities and feet, and a typical palpable skin rash was present in 204 patients (87.2%), which in practical terms allows the clinician to diagnose the disease with great certainty. However, the appearance of slightly less common cutaneous manifestations such as papules, macules or haematomas in combination with a typical rash is also possible. The most severe cutaneous manifestations in the form of ulcerations and necrosis were developed by 11 patients (4.7%), which is in accordance with the literature data (6,7). The exact cause and mechanism of such skin changes in IgAV are not clear, and include trauma, pressure, skin fragility, immune dysregulation, local action of leukocyte esterase and matrix metalloproteinases 2 and 9 (MMP-2 and MMP-9) leading to proteolysis of collagen in the skin (13). Studying the possible connection between more severe cutaneous manifestations and the clinical features of the disease, we noticed that literature data is scarce and contradictory (9,14–16). In this cohort of 234 patients with IgAV, in which 11 (4.7%) developed the most severe cutaneous manifestations, no significant association was observed with other clinical manifestations of the disease, primarily gastrointestinal manifestations and IgAVN.

Several studies have investigated whether there is an association between the prevalence of skin rash and systemic manifestations in IgAV (9–12,17,18). Some studies have shown that cutaneous manifestations spread above the waist level significantly increase the risk of gastrointestinal system involvement (9,11,12) and the development of IgAVN (9,10,17), while studies conducted on a group of adult patients with IgAV showed significant association with the development of arthritis (17). On the other hand, Poterucha et al did not find a connection between the prevalence of skin rash and systemic manifestations in IgAV (18). We observed that patients with purpuric rash spread above the waist have more frequently affected gastrointestinal system and a higher incidence of IgAVN. Another association between cutaneous manifestations spread over the lower extremities and IgAVN is manifested in the higher frequency of proteinuria and the longer time required for the onset of IgAVN. These patients were more likely to undergo invasive procedures such as kidney biopsy. Since the skin rash that has spread

ljenicama i stopalima, a tipičan palpabilni kožni osip sveukupno je imalo 204 bolesnika (87,2%), što u praktičnom smislu kliničaru omogućuje dijagnosticiranje bolesti s velikom sigurnošću. Međutim, moguća je i pojava nešto manje uobičajenih kožnih promjena poput papula, makula ili hematoma u kombinaciji s tipičnim osipom. Najteže kožne promjene u vidu ulceracija i nekroza razvilo je 11 bolesnika (4,7%), što je u skladu s literaturnim podatcima (6,7). Točan uzrok i mehanizam nastanka takvih kožnih promjena u IgAV-u nisu jasni, a uključuju traumu, pritisak, fragilitet kože, imunološku disregulaciju, lokalno djelovanje leukocitne esteraze i matriks metaloproteinaza 2 i 9 (MMP-2 i MMP-9) koje dovode do proteolize kolagena u koži (13). Proučavajući moguću povezanost težih kožnih manifestacija s kliničkim osobitostima bolesti uočili smo da su literaturni podatci oskudni i kontradiktorni (9,14-16). U ovoj kohorti od 234 bolesnika s IgAV-om, u kojoj je njih 11 (4,7%) razvilo najteže kožne promjene, nije uočena značajna povezanost s drugim kliničkim manifestacijama bolesti, ponajprije gastrointestinalnim manifestacijama i IgAVN-om.

Više istraživanja je ispitivalo postoji li povezanost između rasprostranjenosti kožnog osipa i sistemskih manifestacija u IgAV-u (9-12,17,18). Neka istraživanja pokazala su da kožne promjene raširene iznad razine struka značajno povećavaju rizik za zahvaćanje gastrointestinalnog sustava (9,11,12) i razvoj IgAVN-a (9,10,17), dok su istraživanja provedena na skupini odraslih bolesnika s IgAV-om pokazala značajniju povezanost s razvojem artritisa (17). S druge strane, Poterucha i suradnici nisu pronašli vezu između rasprostranjenosti kožnog osipa i sistemskih manifestacija u IgAV-u (18). U našoj kohorti bolesnika također je uočeno da bolesnici s kožnim osipom proširenim iznad donjih udova imaju češće zahvaćen gastrointestinalni sustav i veću pojavnost IgAVN-a. Druga povezanost između kožnih promjena proširenih iznad donjih udova i IgAVN-a očituje se i u većoj učestalosti proteinurije i duljem vremenu potrebnom za nastanak IgAVN-a. Ovi bolesnici bili su češće podvrgnuti invazivnim postupcima poput biopsije bubrega. Budući da kožni osip koji se proširio od donjih udova i gluteusa na ruke, trup i lice označava da upalni proces u malim krvnim žilama tinja uz kontinuirano otpuštanje medijatora upale, čini se logičnim zaključiti da takvi bolesnici s većom učestalošću razvijaju gastrointestinalne manifestacije i IgAVN, imaju značajno dulju hospitalizaciju, kao i potrebu za liječenjem sistemskim glukokortikoidima i antihipertenzivnim lijekovima. Prema SHARE (engl. *Single-Hub Access for Pediatric Rheumatology in Europe*) preporukama peroralni prednizolon indiciran je u liječenju blagog i umjerenog IgAVN-a, dok je antihipertenzive iz skupine inhibitora angiotenzin konvertaze poželjno uključiti u svih bolesnika u kojih se u sklopu IgAVN-a pojavila proteinurija radi povoljnog učinka na prevenciju ili ograničavanje sekundarnoga

from the lower extremities and the gluteal region to the arms, trunk and face indicates that the inflammatory process in small blood vessels is developing with the continuous release of inflammatory mediators, it seems logical to conclude that such patients develop gastrointestinal manifestations and IgAVN with greater frequency, have significantly longer hospitalization time, and require treatment with systemic glucocorticoids and antihypertensive drugs. According to the recommendations of the Single Hub and Access Point for Pediatric Rheumatology in Europe (SHARE), oral prednisolone is indicated in the treatment of mild and moderate IgAVN, while antihypertensives from the group of angiotensin-converting enzyme inhibitors should preferably be included in the treatment of all patients in whom proteinuria has appeared as part of IgAVN for the sake of achieving a favourable effect on the prevention or limitation of secondary glomerulonephritis (8). Although the SHARE recommendations do not specify any guidelines for the treatment of spread cutaneous manifestations as well as the most severe ones, most of our patients received systemic glucocorticoids in such cases, especially patients with ulcerations and necrosis. Since in a large number of patients the diagnosis of IgAV is already clear on the basis of the clinical features, a skin biopsy is rarely indicated. This is also indicated by the SHARE recommendations, according to which a skin biopsy is required in the case of an atypical rash to exclude other diagnoses, especially ANCA-associated vasculitis, which in older children may present with symptoms and signs compatible with IgAV at the onset of the disease. In case there is an indication for a skin biopsy, it should be done at the site of the newly appeared cutaneous manifestations (8). In our study, a skin biopsy was performed in only one patient with severe cutaneous manifestations and an atypical appearance of a purpuric rash. Therefore, it can be said that skin biopsy in children with IgAV is an exception rather than the rule. The follow-up of all patients was performed for at least 6 months and all of them recovered from the cutaneous manifestations, except for one patient with ulcerations who developed scars. Ten patients are still under clinical follow-up and treated for IgAVN.

The main limitation of this paper is the retrospective nature of the research, as well as the small number of patients with the most severe cutaneous manifestations in the form of ulcerations and necrosis, on the basis of which recommendations related to therapy and follow-up of such patients could be made, which certainly remains one of the future challenges. Nevertheless, we gave an overview of the cutaneous manifestations of the most common childhood vasculitis in the Republic of Croatia, in which we observed that the frequency of severe cutaneous manifestations in IgAV is less frequent than the standard clinical features of glomerularnog oštećenja (8). Premda u SHARE preporukama nisu navedene smjernice za liječenje proširenih kožnih promjena kao i onih najtežih, većina naših bolesnika i u takvim je slučajevima dobivala sistemske glukokortikoide, osobito bolesnici s ulceracijama i nekrozama. Budući da je u velikog broja bolesnika dijagnoza IgAV-a jasna već na osnovi kliničke slike, biopsija kože rijetko je indicirana. O tome također govore i SHARE preporuke prema kojima je biopsija kože potrebna u slučaju atipičnog osipa kako bi se isključile druge dijagnoze, osobito vaskulitisi povezani s ANCA-om koji se u starije djece u početku bolesti mogu očitovati simptomima i znakovima kompatibilnim s IgAV-om. U slučaju da postoji indikacija za biopsiju kože, ona se treba napraviti na mjestu najsvježijih kožnih promjena (8). U našem istraživanju biopsija kože je učinjena u samo jednog bolesnika s teškim kožnim promjenama i atipičnim izgledom purpuričnog osipa. Stoga se može reći da je biopsija kože u djece s IgAV-om izuzetak, a ne pravilo. Svi bolesnici praćeni su barem šest mjeseci i kod svih je došlo do oporavka kožnih promjena, osim u jednog bolesnika s ulceracijama koji je razvio ožiljke. Deset bolesnika i nadalje se klinički prati i liječi zbog IgAVN-a.

Glavno ograničenje u ovom radu retrospektivna je priroda istraživanja kao i mali broj bolesnika s najtežim kožnim manifestacijama u vidu ulceracija i nekroza, na osnovi čega bi se mogle donijeti preporuke vezane uz terapiju i praćenje takvih bolesnika, što svakako ostaje jedan od budućih izazova. Ipak, dali smo pregled kožnih manifestacija najčešćeg vaskulitisa dječje dobi u Republici Hrvatskoj u kojem smo uočili da je učestalost teških kožnih promjena u IgAV-u rjeđa od klasične slike purpuričnog osipa i/ili petehija. Također smo uočili da su bolesnici s kožnim osipom koji se proširio od donjih udova na ruke, trup i lice imali češće sistemske manifestacije bolesti, odnosno češće zahvaćen gastrointestinalni sustav i veću pojavnost IgAVN-a, što svakako nalaže pomnije kliničko praćenje takvih bolesnika kako bi se na vrijeme prepoznale i liječile moguće komplikacije IgAV-a.

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purpuric rash and/or petechiae. We also observed that patients with a skin rash that spread from the lower extremities to the hands, trunk and face had more frequent systemic manifestations of the disease, i.e. more often the gastrointestinal system was involved along with a higher incidence of IgAVN, which certainly requires a closer clinical follow-up of such patients in order for the possible complications of IgAV to be recognized and treated in time.

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