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CLINICAL AND LABORATORY FEATURES OF IgA VASCULITIS WITH GASTROINTESTINAL INVOLVEMENT: A 12-YEAR EXPERIENCE OF THE REFERRAL CENTRE FOR PAEDIATRIC AND ADOLESCENT RHEUMATOLOGY OF THE REPUBLIC OF CROATIA

KLINIČKE I LABORATORIJSKE ZNAČAJKE IgA VASKULITISA S GASTROINTESTINALNOM ZAHVAĆENOŠĆU: DVANAESTOGODIŠNJE ISKUSTVO REFERENTNOG CENTRA ZA PEDIJATRIJSKU I ADOLESCENTNU REUMATOLOGIJU REPUBLIKE HRVATSKE

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Abstract

Introduction. IgA vasculitis (IgAV) is the most common systemic vasculitis in childhood. More than half of IgAV patients experience gastrointestinal involvement which usually occurs in the form of abdominal pain, nausea and vomiting, and up to 5% of patients may develop serious complications such as intussusception, intestinal perforation and / or acute bleeding. The aim of our study was to determine the clinical and laboratory features of gastrointestinal involvement in IgAV. *Materials and methods.* Retrospective analysis of IgAV patients' data, who were 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 2009 to 2020, and who experienced gastrointestinal involvement. Differences between categorical variables were examined using the $\chi 2$ test, and between the numerical ones using the Mann-Whitney U-test. *Results.* IgAV was diagnosed in 216 patients, 116 boys and 100 girls. Gastrointestinal involvement was detected in 94 patients (43.5%), the age range at diagnosis was 6.75 (5.2 – 9), and the M : F ratio was 1.68 : 1. The most common clinical sign of gastrointestinal involvement in IgA vasculitis was abdominal pain which occurred in 45 patients (47.9%). Abdominal pain was most often located in the periumbilical region (62.5%). One patient developed ileocolic intussusception. The incidence of generalised purpuric rash ($p = 0,023$) and nephritis ($p = 0,001$) was higher in patients with gastrointestinal involvement compared to a group of patients without gastrointestinal involvement. This group of

patients had statistically significantly higher values of leukocyte count (p = 0,021) and lower values of erythrocyte sedimentation rate (p = 0,039) and total serum proteins (p = 0,002). In the majority of cases, patients with gastrointestinal involvement were male (p = 0,019), their length of stay (LoS) in the hospital was longer (p < 0,001) and they had a higher frequency of relapses (p = 0,011). *Conclusion.* In conclusion, gastrointestinal symptoms in IgAV are most often self-limiting, while complications are rare. We observed that, in most cases, patients with gastrointestinal symptoms were males, with longer length of stay in the hospital, and a higher frequency of nephritis and relapses.

Key words: Henoch-Schönlein purpura; Vasculitis; Gastrointestinal tract; Children; Adolescents

Sažetak

Uvod. IgA vaskulitis (IgAV) najčešći je sistemski vaskulitis dječje dobi. U više od polovice bolesnika s IgAV-om dolazi do zahvaćanja gastrointestinalnog sustava najčešće u vidu bolova u trbuhu, mučnine i povraćanja, a u do 5% bolesnika mogu se razviti ozbiljne komplikacije poput intususcepcije, perforacije crijeva i/ili akutnog krvarenja. Cilj istraživanja bio je utvrditi kliničke i laboratorijske značajke zahvaćenosti gastrointestinalnog sustava u IgAV-u. *Materijali 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 2009. do 2020. godine, koji su imali zahvaćen gastrointestinalni sustav. Razlike između kategorijskih varijabla ispitane su pomoću $\chi 2$ testa, a one između numeričkih Mann-Whitneyevim U-testom. *Rezultati.* IgAV je dijagnosticiran u 216 bolesnika, od toga 116 dječaka i 100 djevojčica. Gastrointestinalni sustav bio je zahvaćen u 94 bolesnika (43,5%), raspon dobi u trenutku dijagnoze bio je 6,75 (5,2–9) godina, a omjer M:Ž 1,68:1. Najčešći klinički znak zahvaćanja gastrointestinalnog sustava u IgA vaskulitisu bila je bol u trbuhu koju je imalo 45 bolesnika (47,9%). Bolovi u trbuhu bili su najčešće locirani periumbilikalno (62,5%). Jedan bolesnik razvio je ileokoličnu invaginaciju crijeva. Učestalost generaliziranoga purpuričnog osipa (p=0,023) i pojave nefritisa (p=0,001) bila je veća u bolesnika sa zahvaćenim gastrointestinalnim sustavom u usporedbi sa skupinom bolesnika bez zahvaćenog gastrointestinalnog sustava. Ta skupina bolesnika imala je statistički značajno veći broj leukocita (p=0,021) te niže vrijednosti sedimentacije eritrocita (p=0,039) i ukupnih proteina (p=0,002). Bolesnici sa zahvaćenim gastrointestinalnim sustavom češće su bili muškog spola (p=0,019), imali su dulje trajanje hospitalizacije (p<0,001) i veću učestalost relapsa (p=0,011). *Zaključak.* Zaključno, gastrointestinalni simptomi u IgAV-u najčešće su samoograničavajući, a komplikacije rijetke. Uočili smo da su bolesnici s gastrointestinalnim simptomima IgA vaskulitisa češće muškog spola, imaju duže trajanje hospitalizacije te veću pojavu nefritisa i relapsa.

Ključne riječi: purpura, Schoenlein-Henoch, vaskulitis, gastrointestinalni sustav, djeca, adolescenti

INTRODUCTION

IgA vasculitis (IgAV), formerly known as Henoch-Schönlein purpura (HSP), is a systemic, IgA-mediated vasculitis that mainly affects children but can also occur in adults (1). It is the most common vasculitis in childhood, with an average annual incidence in the Republic of Croatia of 6.79 per 100,000 children (2). According to the 2008 EULAR/PRINTO/PRES criteria, the diagnosis of IgAV requires the presence of palpable non-thrombocytopenic purpura with at least one of four other symptoms or signs of the disease: abdominal pain, histopathological signs of leukocytoclastic vasculitis with predominant IgA deposition, arthritis/arthralgia, and renal involvement in the form of haematuria and / or proteinuria (1,3). In children diagnosed with IgAV, gastrointestinal involvement usually occurs within a week of the onset of purpuric rash and can sometimes occur up to two weeks prior to the onset of rash (4). According to our literature review, gastrointestinal involvement ranges between 50% and 75% (4–7), and it is most often manifested by abdomi-

UVOD

Henoch-Schönleinova purpura (HSP) ili IgA vaskulitis (IgAV), kako se danas naziva, sistemski je, IgA-posredovan vaskulitis koji uglavnom zahvaća djecu, ali se može pojaviti i u odraslih (1). To je najčešći vaskulitis dječje dobi s prosječnom godišnjom incidencijom u Republici Hrvatskoj od 6,79 na 100.000 djece (2). Prema EULAR/PRINTO/PRES kriterijima iz 2008. za dijagnozu IgAV-a neophodno je postojanje palpabilne netrombocitopenične purpure uz prisutnost barem još jednog od četiriju simptoma ili znaka bolesti: bol u trbuhu, patohistološki znakovi leukocitoklastičnog vaskulitisa s predominantnim IgA depozitima, artritis/artralgije i zahvaćanje bubrega u vidu hematurije i/ili proteinurije (1,3). U djece s IgAV-om zahvaćenost gastrointestinalnog sustava obično nastupi unutar tjedan dana nakon pojave purpuričnog osipa, a katkad može prethoditi osipu i do dva tjedna (4). Prema dostupnim literaturnim podatcima, zahvaćenost gastrointestinalnog sustava kreće se između 50% i 75% (4–7), a klinički se najčešće očituje bolovima u trbuhu, mučninom,

nal pain, nausea, vomiting, and blood and mucus in the stool (4–6). Abdominal pain is most often located in the periumbilical region and in the epigastrium, it intensifies after meals, and is caused by submucosal haemorrhage and intestinal oedema, which results in the exudation of interstitial fluid and blood into the lumen of the gastrointestinal tract (4–6). Although IgAV is most often a self-limiting disease that resolves spontaneously, up to 5% of patients may experience serious gastrointestinal complications, most commonly intussusception, intestinal perforation, and major haemorrhage (4–7). The importance of early recognition of these complications is that they also require surgical intervention, because otherwise they could be life-threatening and even fatal (4,5). Numerous laboratory, microbiological, ultrasound and radiological tests are used in the diagnosis of IgAV with gastrointestinal involvement, in addition to the clinical features which are the key element in making the diagnosis. This study includes 94 IgAV patients with gastrointestinal involvement, who were treated at the Department of Paediatrics of the University Hospital Centre Zagreb in the last 12 years. The aim of this study is to present and compare the clinical and laboratory features, treatment methods, disease course and outcome in the case of IgAV patients with gastrointestinal involvement compared to other IgAV patients.

SUBJECTS AND METHODS

A retrospective study was conducted involving patients diagnosed with IgAV in the period from January 2009 to June 2020 at the Division of Clinical Immunology, Allergology and Rheumatology, Department of Paediatrics, University Hospital Centre Zagreb, Referral Centre for Paediatric and Adolescent Rheumatology of the Ministry of Health of the Republic of Croatia. All patients were under the age of 18 and met the EULAR/PRINTO/PRES criteria for the diagnosis of IgAV (3). Epidemiological, clinical, and laboratory data on IgAV patients were collected from a database based on medical records, which enabled the long-term follow-up of patients. The research was approved by the Ethics Committee of the University Hospital Centre Zagreb and the School of Medicine, University of Zagreb. Demographic data included age at diagnosis of IgAV, sex, and date of diagnosis. Clinical data included the length of stay in the hospital (LoS), the presence of previous infection, the order of onset of symptoms, the prevalence of purpuric rash, organ involvement, type of medication, outcome, and number of relapses. Disease relapse was defined as the recurrence of symptoms and signs characteristic of IgAV after an asymptomatic period of at least one month. The laboratory findings that were analysed included inflammatory markers (erythrocyte sedimentation rate, C-reactive protein and ferritin), complete

povraćanjem te krvlju i sluzi u stolici (4–6). Bolovi u trbuhu najčešće su smješteni periumbilikalno i u epigastriju, pojačavaju se nakon jela, a uzrok im je submukozno krvarenje i edem probavne stijenke, što dovodi do izlaska intersticijske tekućine i krvi u lumen probavne cijevi (4–6). Premda je IgAV najčešće samoograničavajuća bolest koja i spontano prođe, u do 5% bolesnika mogu se javiti ozbiljne komplikacije vezane uz gastrointestinalni sustav, među kojima su najčešće intususcepcija, perforacija crijeva i masivno krvarenje (4–7). Važnost ranog prepoznavanja navedenih komplikacija jest u tome što one zahtijevaju i kiruršku intervenciju, jer u suprotnom može doći do životne ugroze bolesnika pa i smrtnog ishoda (4,5). U dijagnostici IgAV-a s gastrointestinalnom zahvaćenošću, uz kliničku sliku kao ključnu u postavljanju dijagnoze, koriste se brojne laboratorijske, mikrobiološke, ultrazvučne i radiološke pretrage. U ovom radu prikazujemo 94 bolesnika s IgAV-om u kojih je bio zahvaćen gastrointestinalni sustav, a liječili su se u Klinici za pedijatriju Kliničkoga bolničkog centra Zagreb u posljednjih 12 godina. Cilj rada je prikazati i usporediti kliničku sliku, laboratorijske značajke, liječenje, tijek bolesti i ishod IgAV-a s gastrointestinalnom zahvaćenošću u odnosu na preostale bolesnike s IgAV-om.

ISPITANICI I METODE

Provedeno je retrospektivno istraživanje u koje su uključeni bolesnici kojima je u razdoblju od siječnja 2009. do lipnja 2020. dijagnosticiran IgAV u Zavodu za kliničku imunologiju, reumatologiju i alergologiju Klinike za pedijatriju Kiničkoga bolničkog centra Zagreb, Referentnom centru za pedijatrijsku i adolescentnu reumatologiju Ministarstva zdravstva Republike Hrvatske. Svi bolesnici bili su mlađi od 18 godina i zadovoljili su EULAR/PRINTO/PRES kriterije za dijagnozu IgAV-a (3). Epidemiološki, klinički i laboratorijski podatci o bolesnicima s IgAV-om prikupljeni su iz baze podataka temeljene na medicinskoj dokumentaciji, čime je omogućeno dugoročno praćenje bolesnika. Istraživanje je odobrilo Etičko povjerenstvo Kliničkoga bolničkog centra Zagreb i Medicinskog fakulteta Sveučilišta u Zagrebu. Demografski podatci uključivali su dob pri dijagnozi IgAV-a, spol i datum dijagnoze. Klinički podatci uključivali su trajanje hospitalizacije, postojanje prethodne infekcije, redoslijed pojave simptoma, rasprostranjenost purpuričnog osipa, zahvaćenost organa, vrstu lijekova, ishod i broj relapsa. Relaps bolesti definiran je kao ponovna pojava simptoma i znakova karakterističnih za IgAV nakon asimptomatskog razdoblja u trajanju od najmanje jednog mjeseca. Od laboratorijskih nalaza analizirani su upalni pokazatelji (sedimentacija eritrocita, C-reaktivni protein i feritin), kompletna krvna slika, biokemijske pretrage krvi (kreatinin, ureja, ukupni proteini), koagulacijske

blood count, biochemical blood tests (creatinine, urea, total protein test), coagulation tests (fibrinogen, D-dimer test, prothrombin time test [PT]) and activated partial thromboplastin time [aPTT]) and immunoassays (immunoglobulin classes [IgA, IgG, IgM], antistreptolysin titre [ASOT], total complement measurement [CH50] and complement components C3 and C4). We analysed the presence of haematuria in urine, defined as > 5 erythrocytes in urine sediment, and/or the presence of proteinuria, defined as ≥ 2+ protein in a qualitative urine test strip analysis with the first morning urine sample. In the case of patients with a pathological finding of the first morning urine sample, 24-hour urine protein test was performed. In the 24-hour urine protein test, proteinuria was defined as > 0.15 g/day of total protein excretion. Faecal calprotectin levels and the presence of occult bleeding were analysed in stool samples. Microbiological tests performed on patients with a history of infection included a nasopharyngeal swab. Radiological tests performed on patients with gastrointestinal symptoms included abdominal colour Doppler ultrasound of the ileocecal region.

The data are presented in tabular form, and data preparation was performed using Microsoft Excel. 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 between numerical variables in univariate analysis were analysed using the Mann-Whitney U-test, and between the categorical variables using the $\chi 2$ test. Statistical significance was set at $p < 0.05$.

RESULTS

In the period from January 2009 to June 2020, 216 patients (116 boys and 100 girls) with IgAV were diagnosed at the University Hospital Center Zagreb. The median age (range) at diagnosis was 6.5 (4.5 – 8.4), and the ratio of boys to girls was 1.16 : 1. Purpuric rash was detected in all patients, 155 patients (71.8%) had arthritis/arthralgia, 94 patients (43.5%) experienced gastrointestinal involvement, 45 patients (20.8%) experienced renal involvement, and incidence of scrotal involvement was recorded in 14 boys (12.1%). Two patients (0.9%) developed life-threatening complications such as respiratory distress syndrome and intussusception. In 116 patients (53.7%) the initial presenting symptom of IgAV was purpuric rash, in 66 patients (30.6%) it was arthritis and/or arthralgia, and in 34 patients the initial symptoms were gastrointestinal ones (15.7%). Purpuric rash was generalised in 94 patients (43.5%), and 9 patients (4.2%) experienced severe cutaneous changes in the form of ulcerations and necrosis. The median (range) of renal disease was 4 (0 – 18) days from the diagnosis of IgAV, and renal biopsy was performed in

pretrage (fibrinogen, D-dimeri, protrombinsko vrijeme [PV] i aktivirano parcijalno tromboplastinsko vrijeme [APTV]) te imunološke pretrage (razredi imunoglobulina [IgA, IgG, IgM], antistreptolizinski titar [ASTO], razina ukupnog komplementa [CH50] i komponente komplementa C3 i C4). U urinu je analizirana prisutnost hematurije, definirane kao >5 eritrocita u sedimentu urina i/ili prisutnost proteinurije definirane s ≥2+ proteina u kvalitativnom pregledu urina test-trakom u prvom jutarnjem uzorku urina. U bolesnika s patološkim nalazom prvog jutarnjeg uzorka urina učinjeno je određivanje proteina u 24-satnom urinu. Proteinurija u 24-satnom urinu definirana je kao >0,15 g/dU sveukupno izlučenih proteina. U uzorcima stolice analizirana je razina fekalnog kalprotektina i prisutnost okultnog krvarenja. Mikrobiološke pretrage u bolesnika s anamnezom infekcije uključivale su obrisak nosne sluznice i ždrijela. Od radioloških pretraga u bolesnika s gastrointestinalnim simptomima učinjen je UZV trbuha s obojenim doplerom ileocekalne regije.

Podatci su prikazani tablično, a priprema podataka je izvršena pomoću *Microsoft Office Excela*. Kontinuirane varijable za vrijednosti koje nemaju normalnu distribuciju prikazane su kao medijan i interkvaritilni raspon (od 25 do 75 centile), a kategoričke varijable prikazane su u postotcima. Razlike između grupa u univarijantnoj analizi za numeričke podatke analizirane su pomoću Mann-Whitneyjevog U-testa, a za kategoričke pomoću X^2 testa. Statistička značajnost postavljena je na $p<0,05$.

REZULTATI

U razdoblju od siječnja 2009. do lipnja 2020. u Kliničkom bolničkom centru Zagreb dijagnosticirano je 216 bolesnika s IgAV-om, odnosno 116 dječaka i 100 djevojčica. Medijan (raspon) dobi u trenutku dijagnoze bio je 6,5 (4,5–8,4) godina, a omjer dječaka prema djevojčicama iznosio je 1,16:1. Svi bolesnici imali su purpurični osip, 155 bolesnika (71,8%) imalo je artritis/artralgije, 94 bolesnika (43,5%) imalo je zahvaćen probavni sustav, 45 bolesnika (20,8%) imalo je zahvaćene bubrege, a u 14 dječaka (12,1%) bio je zahvaćen skrotum. Dvoje bolesnika (0,9%) imalo je po život opasne komplikacije u vidu respiratornoga distresnog sindroma i invaginacije crijeva. IgAV je u 116 bolesnika (53,7%) započeo purpuričnim osipom, u 66 bolesnika (30,6%) artritisom i/ili artralgijama, a u 34 bolesnika (15,7%) gastrointestinalnim simptomima. Purpura je u 94 bolesnika (43,5%) bila generalizirana, a 9 bolesnika (4,2%) imalo je teže kožne promjene u vidu ulceracija i nekroza. Medijan (raspon) pojave bubrežne bolesti bio je 4 (0–18) dana od dijagnoze IgAV-a, a biopsija bubrega učinjena je u 23 bolesnika (10,6%). U većini slučajeva IgAV-u je prethodila infekcija (64,8%)

23 patients (10.6%). In most cases, IgAV was preceded by an infection (64.8%) with the most common isolated causes: *Streptococcus pyogenes* (34.4%), *Staphylococcus aureus* (27.8%) and *Streptococcus pneumoniae* (18%). The largest number of patients was diagnosed in winter (31%) and in autumn (26.4%), and the median (range) length of stay (LoS) in the hospital was 10 (5 – 13) days. The most commonly used drugs were glucocorticoids (59.7%) and non-steroidal anti-inflammatory drugs (54.6%). The recurrence of symptoms and signs of IgAV after an asymptomatic period of at least one month was recorded in 31 patients (14.3%).

Gastrointestinal involvement was detected in 94 patients (59 boys and 35 girls). The median age (range) at diagnosis was 6.75 (5.2 – 9), the ratio of boys to girls was 1.68 : 1, and the median length of stay in the hospital was 12 (8 – 16.5) days. In 34 patients (36.2%) gastrointestinal symptoms were preceded by purpuric rash with a median (range) of 3 (2 – 5) days before the onset of the purpuric rash. In 18 patients (19.1%), the purpuric rash and gastrointestinal symptoms occurred simultaneously, while in 42 patients (44.7%), the purpuric rash preceded gastrointestinal symptoms with a median (range) of 3 (1 – 4.25) days before the onset of gastrointestinal symptoms. The most common clinical sign of gastrointestinal involvement in IgA vasculitis was abdominal pain which occurred in 45 patients (47.9%). The other most frequent symptoms included abdominal pain with positive occult bleeding in 22 patients (23.4%) and visible gastrointestinal bleeding (haematemesis, melena, hematochezia) in 16 patients (17%). 10 patients (10.6%) experienced positive occult bleeding without any other symptoms and/or signs of gastrointestinal involvement. One patient developed a severe complication in the form of ileocolic intussusception due to which a surgical procedure had to be performed. Abdominal pain was most often located in the periumbilical region (62.5%) and in the epigastrium (25%). In most cases (62.8%), no abnormalities were detected during the abdominal ultrasound, while in other cases signs of mesenteric lymphadenitis (22.3%) and bowel wall thickening with oedema (14.9%) were detected. In one patient, ileocaecocolic intussusception was detected during the abdominal ultrasound.

Comparing the laboratory findings of IgAV patients, in the group with gastrointestinal involvement, a statistically significant difference in the number of leukocytes (10.8 x 10^9/ L compared to 10.54 x 10^9/ L, p = 0.021), which was higher, was observed, as well as the difference in the values of erythrocyte sedimentation rate (15 mm/hr compared to 20 mm/hr, p = 0.039) and total serum proteins (68 g/L compared to 71 g/L, p = 0.002), which were lower in relation to the group without gastrointestinal involvement. No statistically significant differences were observed in other laboratory

s najčešće izoliranim uzročnicima: *S. pyogenes* (34,4%), *S. aureus* (27,8%) i *S. pneumoniae* (18%). Najveći broj bolesnika dijagnosticiran je zimi (31%) i u jesen (26,4%), a medijan (raspon) trajanja hospitalizacije iznosio je 10 (5–13) dana. Najčešće primjenjivani lijekovi bili su glukokortikoidi (59,7%) i nesteroidni protuupalni lijekovi (54,6%). Ponovnu pojavu simptoma i znakova IgAV-a nakon asimptomatskog razdoblja u trajanju od barem mjesec dana imao je 31 bolesnik (14,3%).

Gastrointestinalni sustav bio je zahvaćen u 94 bolesnika, odnosno 59 dječaka i 35 djevojčica. Medijan (raspon) dobi prilikom dijagnoze bio je 6,75 (5,2–9) godina, omjer dječaka prema djevojčicama 1,68:1, a medijan trajanja hospitalizacije 12 (8–16,5) dana. U 34 bolesnika (36,2%) gastrointestinalni simptomi su prethodili purpuri s medijanom (rasponom) od 3 (2–5) dana prije pojave purpure. U 18 bolesnika (19,1%) purpura i gastrointestinalni simptomi javili su se istodobno, dok je u 42 bolesnika (44,7%) purpura prethodila gastrointestinalnim simptomima s medijanom (rasponom) od 3 (1–4,25) dana prije pojave gastrointestinalnih simptoma. Najčešći klinički znak zahvaćanja gastrointestinalnog sustava u IgAV-u bila je bol u trbuhu koju je imalo 45 bolesnika (47,9%). Sljedeći po učestalosti bili su bolovi u trbuhu s pozitivnim okultnim krvarenjem koje je imalo 22 bolesnika (23,4%) i vidljivo krvarenje iz probavnog sustava (hematemeza, melena, hematokezija) koje je imalo 16 bolesnika (17%). Pozitivno okultno krvarenje bez ikakvih drugih simptoma i/ili znakova zahvaćanja gastrointestinalnog sustava imalo je 10 bolesnika (10,6%). U jednog bolesnika nastala je teška komplikacija u vidu ileokolične invaginacije crijeva, zbog čega je učinjen kirurški zahvat. Bolovi u trbuhu najčešće su bili locirani periumbilikalno (62,5%) i epigastrično (25%). UZV trbuha najčešće je bio uredan (62,8%), zatim sa znacima mezenterijskog limfadenitisa (22,3%) i zadebljanja stijenki crijeva uz edem (14,9%). U jednog bolesnika UZV trbuha pokazao je ileocekokoličnu invaginaciju crijeva.

Uspoređujući laboratorijske nalaze bolesnika s IgAV-om, u skupini sa zahvaćenim gastrointestinalnim sustavom uočena je statistički značajna razlika u broju leukocita (10,8 x 10^9/L u odnosu na 10,54 x 10^9/L, p=0,021) koji je bio viši te u vrijednostima brzine sedimentacije eritrocita (15 mm/h u odnosu na 20 mm/h, p=0,039) i ukupnih serumskih proteina (68 g/L u odnosu na 71 g/L, p=0,002) koje su bile niže u odnosu na skupinu bez zahvaćenog gastrointestinalnog sustava. U preostalim laboratorijskim nalazima nisu uočene statistički značajne razlike. Uočena je statistički značajna razlika u učestalosti generaliziranoga purpuričnog osipa (53,2% u odnosu na 37,7%, p=0,023) kao i pojave nefritisa (30,8% u odnosu na 13,1%, p=0,001) u bolesnika s gastrointestinalnim simptomima. U bolesnika

Table 1. Demographic, clinical and laboratory features in patients with IgA vasculitis with and without gastrointestinal involvement

Tablica 1. Demografske, kliničke i laboratorijske značajke u bolesnika s IgA vaskulitisom sa zahvaćenim gastrointestinalnim sustavom i bez njega

Parameters / Parametri	IgAV patients with GI symptoms / IgAV bolesnici s GI simptomima (N=94)	IgAV patients without GI symptoms / IgAV bolesnici bez GI simptoma (N=122)	p-value* / p-vrijednost*
DEMOGRAPHIC / DEMOGRAFSKI			
Age (in years): median (IQR) / Dob (godine): medijan (IR)	6.7 (5.2–9.0)	6.2 (4.5–7.7)	0.638[b]
Sex (M : F ratio) / Spol (omjer M:Ž)	59:35	57:65	**0.019**[a]
CLINICAL / KLINIČKI			
Length of stay in the hospital (in days): median (IQR) / Hospitalizacija (dani): medijan (IR)	12 (8.0–16.5)	9 (6–11)	**<0.001**[b]
Infection / Infekcija: n (%)	54 (57.4%)	86 (70.5%)	**0.046**[a]
Generalised purpuric rash / Generalizirana purpura: n (%)	50 (53.2%)	46 (37.7%)	**0.023**[a]
Joints / Zglobovi: n (%)	62 (65.9%)	93 (76.2%)	0.096[a]
Kidneys / Bubrezi: n (%)	29 (30.8%)	16 (13.1%)	**0.001**[a]
Time from the diagnosis until the onset of renal disease (in days): median (IQR) / Vrijeme od dijagnoze do pojave bubrežne bolesti (dani): medijan (IR)	4 (0–18)	3 (0–8.7)	**<0.001**[b]
Non-steroidal anti-inflammatory drugs / Nesteroidni antireumatici: n (%)	38 (40.4%)	80 (65.6%)	**<0.001**[a]
Glucocorticoids / Glukokortikoidi: n (%)	74 (78.7%)	55 (45.1%)	**<0.001**[a]
Immunosuppressive drugs / Imunosupresivi: n (%)	8 (8.5%)	4 (3.3%)	0.096[a]
Antihypertensive drugs / Antihipertenzivi: n (%)	16 (17%)	4 (3.3%)	**<0.001**[a]
Relapse / Relaps: n (%)	20 (21.3%)	11 (9%)	**0.011**[a]
LABORATORY / LABORATORIJSKI			
ESR (mm/hr): median (IQR) / SE (mm/h): medijan (IR)	15 (10.8–24.8)	20 (10.5–33.5)	**0.039**[b]
CRP (mg/L): median (IQR) / CRP (mg/L): medijan (IR)	7.5 (2.4–14.8)	5.5 (1.6–14.2)	0.779[b]
Erythrocytes (1012/L): median (IQR) / Eritrociti (10^{12}/L): medijan (IR)	4.7 (4.5–5.1)	4.6 (4.42–4.98)	0.888[b]
Haemoglobin (g/L): median (IQR) / Hemoglobin (g/L): medijan (IR)	129 (120–137)	127 (118–131)	0.083[b]
Leukocytes (109/L): median (IQR) / Leukociti (10^9/L): medijan (IR)	10.8 (8.0–14.3)	10.54 (8.2–12.5)	**0.021**[b]
Thrombocytes (109/L): median (IQR) / Trombociti (10^9/L): medijan (IR)	360 (297–437)	355.5 (277.3–423.5)	0.230[b]
Creatinine (µmol/L): median (IQR) / Kreatinin (µmol/L): medijan (IR)	45.0 (33.3–60.0)	42.5 (32.3–56.3)	0.542[b]
Urea (mmol/L): median (IQR) / Ureja (mmol/L): medijan (IR)	3.9 (3.2–4.7)	4.1 (3.5–4.7)	0.158[b]

findings. A statistically significant difference was observed in the frequency of generalised purpuric rash (53.2% compared to 37.7%, p = 0.023) as well as the occurrence of nephritis (30.8% compared to 13.1%, p = 0.001) in patients with gastrointestinal symptoms. IgAV nephritis was 1.81 times more common in patients with gastrointestinal symptoms (29 patients compared to 16 patients, p = 0.001), and haematuria was twice as common (27.6 % compared to 10.6%, p = 0.001). Patients with gastrointestinal symptoms were more often treated with glucocorticoids (78.7% compared to 45.1%, p < 0.001), while non-steroidal anti-inflammatory drugs were not used as often (40.4% compared to 65.6%, p < 0.001) compared to patients

u kojih su se pojavili gastrointestinalni simptomi 1,81 puta češće je došlo do razvoja nefritisa u sklopu IgAV-a (29 bolesnika u odnosu na 16 bolesnika, p=0,001), a dva puta češći bio je nalaz hematurije (27,6% u odnosu na 10,6%, p=0,001). Bolesnici s gastrointestinalnim simptomima češće su liječeni glukokortikoidima (78,7% u odnosu na 45,1%, p<0,001), a manje nesteroidnim protuupalnim lijekovima (40,4% u odnosu na 65,6%, p<0,001) u usporedbi s bolesnicima koji nisu imali zahvaćen gastrointestinalni sustav. Primjena imunosupresiva bila je dva puta veća, a antihipertenziva iz skupine inhibitora angiotenzin konvertaze čak četiri puta veća u odnosu na bolesnike bez gastrointestinalnih simptoma. Bolesnici s gastrointestinalnim manifesta-

Table 1. Continued / *Tablica 1. Nastavak*

Parameters / Parametri	IgAV patients with GI symptoms / IgAV bolesnici s GI simptomima (N=94)	IgAV patients without GI symptoms / IgAV bolesnici bez GI simptoma (N=122)	p-value* / p-vrijednost*
Ferritin (ng/mL): median (IQR) / Feritin (ng/mL): medijan (IR)	70.5 (48.9–93.4)	67.4 (48.6–105.5)	0.968[b]
PT: median (IQR) / PV: medijan (IR)	0.98 (0.87–1.09)	1.03 (0.94–1.10)	0.984[b]
aPTT (s): median (IQR) / APTV (s): medijan (IR)	25.0 (23.0–26.7)	25.9 (24.5–27.9)	0.400[b]
Fibrinogen (g/L): median (IQR) / Fibrinogen (g/L): medijan (IR)	3.3 (2.7–4.0)	3.4 (2.9–4.0)	0.624[b]
D-dimer test (µg/L): median (IQR) / D-dimeri (µg/L): medijan (IR)	2.46 (0.71–4.89)	2.12 (0.99–4.23)	0.803[b]
Total protein test (g/L): median (IQR) / Ukupni proteini (g/L): medijan (IR)	68 (65.00–71.25)	71 (67–74)	**0.002**[b]
Albumin test (g/L): median (IQR) / Albumini (g/L): medijan (IR)	37.9 (34.7–40.6)	39.2 (36.5–42.6)	0.384[b]
IgA (g/L): median (IQR) / IgA (g/L): medijan (IR)	1.99 (1.31–2.63)	1.84 (1.37–2.36)	0.674[b]
IgG (g/L): median (IQR) / IgG (g/L): medijan (IR)	9.39 (7.61–11.44)	10.11 (8.62–12.33)	0.516[b]
IgM (g/L) median (IQR) / IgM (g/L) medijan (IR)	0.84 (0.68–1.12)	0.97 (0.74–1.31)	0.568[b]
ASOT: median (IQR) / ASTO: medijan (IR)	135.5 (32.3–417.3)	202 (37.0–452.5)	0.294[b]
C_3 (g/L): median (IQR) / C_3 (g/L): medijan (IR)	1.26 (1.08–1.38)	1.31 (1.16–1.43)	0.575[b]
C_4 (g/L): median (IQR) / C_4 (g/L): medijan (IR)	0.25 (0.20–0.30)	0.25 (0.20–0.32)	0.818[b]
Faecal calprotectin (µg/g): median (IQR) / Fekalni kalprotektin (µg/g): medijan (IR)	24 (20.0–72.5)	30 (20–49)	0.718[b]
24-hour urine protein test (g/day): median (IQR) / 24-satna proteinurija (g/dU: medijan (IR)	0.11 (0.07–0.30)	0.09 (0.06–0.16)	0.772[b]
Haematuria > 5 erythrocytes per high-power field and / or 2+ on a dipstick test: n (%) / Hematurija >5 eritrocita u vidnom polju i/ili 2+ na *dipstick* testu: n (%)	26 (27.6%)	13 (10.6%)	**0.001**[a]
Positive faecal occult blood test (+/–): n (number) / Stolica pozitivna na okultno krvarenje (+/–): n (broj)	48	0	N/A

IQR/IR: interquartile range / interkvartilni raspon; IgAV: IgA vasculitis / IgA vaskulitis; GI: gastrointestinal / gastrointestinalni; ESR/SE: erythrocyte sedimentation rate / sedimentacija eritrocita; CRP: C-reactive protein / C-reaktivni protein; 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; ASOT/ASTO: anti-streptolysin O titre / antistreptolizinski titar; C_3: complement component C_3 / C_3 komponenta komplementa; C_4: complement component C_4 / C_4 komponenta komplementa; NSAIDs/NSAID: non-steroidal anti-inflammatory drugs / nesteroidni protuupalni lijekovi; N/A: not applicable / nije primjenjivo

*Podatci su prikazani kao medijan (interkvartilni raspon) i u postotcima, statistička značajnost postavljena na *P<0,05 / Data was presented as the median range (interquartile range) and in percentages, statistical significance was set to *p < 0.05; [a]χ^2 test, [b]Mann-Whitney U-test/ Mann-Whitneyjev U-test*

without gastrointestinal involvement. The use of immunosuppressive drugs was twice as high, and the use of antihypertensive drugs from the group of angiotensin-converting enzyme (ACE) inhibitors was as much as four times higher than in patients without gastrointestinal symptoms. Patients with gastrointestinal manifestations had a lower incidence of infections that preceded the occurrence of IgA vasculitis (57.4% compared to 70.5%, p = 0.046). The incidence of IgAV relapse in patients with gastrointestinal symptoms was 1.81 times higher compared to patients without gastrointestinal involvement (21.3% compared to 9%, p = 0.011). When it comes to demographic parameters, a statistically significant difference was observed in gas-

cijama imali su manju pojavnost infekcija koje su prethodile pojavi IgA vaskulitisa (57,4% u odnosu na 70,5%, p=0,046). Učestalost relapsa IgAV-a u bolesnika s gastrointestinalnim simptomima bila je 1,81 puta veća u usporedbi s bolesnicima bez zahvaćenosti gastrointestinalnog sustava (21,3% u odnosu na 9%, p=0,011). Od demografskih pokazatelja uočena je statistički značajna razlika u zahvaćanju gastrointestinalnog sustava u muškog spola (62,7% u odnosu na 46,7%, p=0,019) (tablica 1).

RASPRAVA

U ovom retrospektivnom istraživanju koje je provedeno tijekom dvanaestogodišnjeg razdoblja u Klinici za

trointestinal involvement in males (62.7% compared to 46.7%, p = 0.019) (Table 1).

DISCUSSION

In this retrospective study, which was conducted during a twelve-year period at the Department of Paediatrics of the University Hospital Centre Zagreb, the clinical and laboratory features of IgA vasculitis patients with gastrointestinal involvement were analysed. Gastrointestinal symptoms are present in most IgAV patients, and their incidence ranges from 50% to 75% (4–7). In addition to that, acute complications that can occur with this disease are most often associated with gastrointestinal involvement, and they can also be life-threatening and require surgical treatment (4,5,8). Our study shows that the number of patients with gastrointestinal symptoms falls within the average range described in other studies (43.5%) (9 – 11). In observing patients with gastrointestinal symptoms, a statistically significant difference was observed in the more frequent involvement of male patients (p = 0.019), which is in line with the data reported in the reviewed literature (4,12,13). Patients with gastrointestinal involvement had a higher incidence of generalised purpuric rash, that is, purpura occurring on both extremities (14–16). The most significant results in the clinical sense are related to the fact that patients with gastrointestinal symptoms were more often prone to developing IgAV nephritis, which is the most important chronic complication of the disease that can result in chronic kidney failure in 1 – 15% of patients (17–20). In our cohort of patients, the incidence of nephritis was 1.81 times higher in the group of patients who had at least one gastrointestinal symptom. Another connection between the gastrointestinal system and kidneys was the higher incidence of microhematuria in patients with gastrointestinal symptoms, who were more frequently treated with glucocorticoids, immunosuppressive drugs and antihypertensive drugs and had a longer length of stay in the hospital (p < 0.001) (4,12). The connection between gastrointestinal and renal involvement in IgAV has been described in some studies, but the results are ambiguous (13,18,21,22). The pathophysiological mechanism that could explain the increased incidence of nephritis in patients with gastrointestinal symptoms remains unknown. However, from this observation it is important to point out that patients who have experienced gastrointestinal manifestations may have a higher risk of developing nephritis. In this regard, the issue of the optimal length of follow-up of these patients has not yet been resolved to ensure the timely separation of the patients who have developed nephritis (18). In the treatment of IgAV patients with gastrointestinal involvement, there are conflicting opinions of various authors (23–25) about the use of glucocorticoids. Accordpedijatriju Kliničkoga bolničkog centra Zagreb analizirane su kliničke i laboratorijske značajke bolesnika s IgA vaskulitisom koji su imali zahvaćen gastrointestinalni sustav. Gastrointestinalni simptomi prisutni su u većine bolesnika s IgAV-om, a njihova se učestalost prema literaturnim podacima kreće između 50% i 75% (4–7). Osim toga, upravo su sa zahvaćanjem gastrointestinalnog sustava najčešće povezane akutne komplikacije koje se pojavljuju u ovoj bolesti, a koje mogu dovesti do životne ugroze bolesnika te zahtijevati kirurško liječenje (4,5,8). Iz našeg je istraživanja razvidno da je broj bolesnika s gastrointestinalnim simptomima u okviru prosjeka koji je opisan i u drugim istraživanjima (43,5%) (9–11). Uočena je statistički značajna razlika u češćem zahvaćanju muškog spola u bolesnika s gastrointestinalnim simptomima (p=0,019), što je u skladu s literaturnim podatcima (4,12,13). Bolesnici sa zahvaćenim gastrointestinalnim sustavom imali su veću pojavu generaliziranoga purpuričnog osipa, odnosno purpure proširene na oba ekstremiteta (14–16). Klinički najznačajniji rezultati vezani su uz činjenicu da su bolesnici u kojih su se pojavili gastrointestinalni simptomi u konačnici češće razvili nefritis u sklopu IgAV-a, što je najvažnija kronična komplikacija bolesti koja može rezultirati kroničnim zatajenjem bubrega u 1–15% bolesnika (17–20). U našoj kohorti bolesnika učestalost nefritisa bila je 1,81 puta veća u skupini bolesnika koji su imali barem jedan gastrointestinalni simptom. Druga povezanost između gastrointestinalnog sustava i bubrega očitovala se u većoj učestalosti mikrohematurije u bolesnika s gastrointestinalnim simptomima, a ti su bolesnici češće liječeni glukokortikoidima, imunosupresivima i antihipertenzivima te su imali dulje trajanje hospitalizacije (p<0,001) (4,12). Povezanost zahvaćanja probavnog sustava i bubrega u IgAV-u opisana je u nekim istraživanjima, ali rezultati nisu jednoznačni (13,18, 21,22). Patofiziološki mehanizam kojim bi se objasnila povećana učestalost nefritisa u bolesnika koji su imali prisutne gastrointestinalne simptome nije poznat. No, iz ovog opažanja važno je istaknuti kako bi bolesnici u kojih su se pojavile gastrointestinalne manifestacije mogli imati veći rizik za razvoj nefritisa. S tim u svezi, još nije riješeno pitanje optimalne duljine praćenja ovih bolesnika kako bi se na vrijeme izdvojili oni u kojih je došlo do pojave nefritisa (18). U liječenju bolesnika s IgAV-om koji imaju zahvaćen gastrointestinalni sustav postoje oprečna razmišljanja različitih autora (23–25) o primjeni glukokortikoida pa tako prema jednima glukokortikoidi značajno smanjuju bol, trajanje hospitalizacije i sprječavaju nastanak komplikacija (24), dok drugi nisu primijetili značajno smanjenje rizika u ponovnom javljanju gastrointestinalnih simptoma (25). Prema preporukama SHARE (engl. *Single-Hub Access for Pediatric Rheumatology in Europe*) glukokortikoidi su indicirani kratkotrajno i/ili u slučajevima ozbiljnoga

ing to some, glucocorticoids significantly reduce pain, length of stay in the hospital and prevent the development of complications (24), while others did not notice a significant reduction in risk of recurrence of gastrointestinal symptoms (25). According to the recommendations of the SHARE initiative (Single-Hub Access for Paediatric Rheumatology in Europe) glucocorticoids are indicated for short-term use and/or in cases of severe gastrointestinal bleeding (26). Out of a total of 94 patients with gastrointestinal symptoms, 74 (78.7%) were treated with glucocorticoids, and 20 of them had a recurrence of IgAV, most often in the form of purpuric rash, so, in our experience, the short-term use of glucocorticoids in patients with severe gastrointestinal manifestations proved to be effective. In addition to the fact that our patients with gastrointestinal involvement were more often treated with glucocorticoids, they also received antihypertensive therapy with angiotensin-converting enzyme (ACE) inhibitors, as the majority of patients in this group were those with nephritis, and, according to the recommendations of the SHARE initiative, it is advisable to use this type of therapy in all patients who have developed proteinuria as a result of nephritis due to the beneficial effect on the prevention or limitation of secondary glomerular disease (26). Clinical manifestations of gastrointestinal involvement in IgA vasculitis most often include nausea, vomiting and abdominal pain (cramping), which is most often present in the periumbilical region and the epigastrium (3–5). Furthermore, in our patient cohort, the clinical features of most of our patients, 67 of them (31%), included abdominal pain in the periumbilical region. Gastrointestinal bleeding occurred in 48 patients (22.2%), which is also within the expected frequency of this manifestation, which otherwise occurs in the range from 18 to 52% (4–7,12). Bleeding was mostly occult, and the follow-up of patients with positive occult bleeding lasted for the next six months, with no cases of recurrence of blood in the stool. In 34 patients (15.7%) gastrointestinal symptoms had occurred prior to the onset of the characteristic purpuric rash, with a median of three days, similar to other studies, although the gastrointestinal symptoms may precede the onset of purpura by up to two weeks (4,5,8,27– 29). This is often a differential diagnostic problem because it mimics the acute abdomen, which often includes surgical intervention (8,27,29). Only one patient (0.5%) had to undergo surgery, as he developed ileocaecocolic intussusception, so, it can be concluded that the most severe gastrointestinal complications in our study were extremely rare. In the reviewed literature, intussusception is mentioned as the most common complication related to the gastrointestinal system with an incidence of 0.7–13.6% (4,5). Among the imaging tests, an ultrasound and a CT scan are the most used methods (4–6,30). According to

gastrointestinalnog krvarenja (26). Od 94 naša bolesnika s gastrointestinalnim simptomima njih 74 (78,7%) liječeno je glukokortikoidima, a od toga ih je 20 imalo ponovnu pojavu IgAV-a i to najčešće u vidu purpure, tako da se prema našim iskustvima kratkotrajna primjena glukokortikoida u bolesnika s težim gastrointestinalnim manifestacijama pokazala učinkovitom. Osim što su naši bolesnici sa zahvaćenim gastrointestinalnim sustavom češće liječeni glukokortikoidima, oni su češće primali i antihipertenzivnu terapiju inhibitorima angiotenzin konvertaze, budući da su se u toj skupini bolesnika češće nalazili oni s nefritisom, a prema preporukama SHARE poželjno je takvu terapiju uključiti u svih bolesnika u kojih se u sklopu nefritisa pojavila proteinurija radi povoljnog učinka na prevenciju ili ograničavanje sekundarnoga glomerularnog oštećenja (26). Klinički se zahvaćanje gastrointestinalnog sustava u IgA vaskulitisu najčešće očituje mučninom, povraćanjem i grčevitim bolovima u trbuhu koji su najčešće locirani epigastrično i periumbilikalno (3–5), a i u našoj kohorti bolesnika najveći broj, njih 67 (31%), imao je kliničku sliku periumbilikalnih bolova u trbuhu. Gastrointestinalno krvarenje pojavilo se u 48 bolesnika (22,2%), što je također u okviru očekivane učestalosti ove manifestacije koja se inače pojavljuje u rasponu od 18 do 52% (4–7,12). Krvarenje je većinom bilo okultno, a bolesnici s pozitivnim okultnim krvarenjem praćeni su kroz sljedećih šest mjeseci, pri čemu niti u jednom slučaju nije došlo do ponovne pojave krvi u stolici. U 34 bolesnika (15,7%) gastrointestinalni simptomi prethodili su pojavi karakterističnoga purpuričnog osipa, s medijanom od tri dana, slično kao i u ostalim istraživanjima, iako gastrointestinalni simptomi mogu prethoditi pojavi purpure i do dva tjedna (4,5,8,27–29). Navedeno često predstavlja i diferencijalno-dijagnostički problem jer oponaša akutni abdomen koji onda nerijetko uključuje i kiruršku intervenciju (8,27,29). Samo jedan bolesnik (0,5%) liječen je kirurški, budući da je razvio ileocekokoličnu invaginaciju crijeva, pa se prema tome može zaključiti da su najteže gastrointestinalne komplikacije u našem istraživanju bile iznimno rijetke. U literaturi se kao najčešća komplikacija vezana uz gastrointestinalni sustav upravo i spominje intususcepcija s učestalošću 0,7–13,6% (4,5). Od slikovnih pretraga najčešće korištene metode jesu ultrazvučna i CT dijagnostika (4–6,30). Prema većini autora, ultrazvučna dijagnostika je prvi izbor u otkrivanju crijevnog vaskulitisa među slikovnim metodama zbog svoje neinvazivnosti i sigurne primjene, što je osobito važno u dječjoj populaciji (4,5,30). Znakovi zadebljanja crijevne stijenke uz edem sluznice ultrazvučno izgledaju poput ograničenih hipoehogenih polumjeseca, a obojenim doplerom u zahvaćenom dijelu crijeva detektira se smanjeni protok (4,5,30). Još jedna prednost ultrazvuka jest mogućnost procjene količine intraabdominalne tekućine i

most authors, diagnostic ultrasound is the first choice in the detection of intestinal vasculitis among other imaging methods due to its non-invasiveness and safe use, which is especially important in the paediatric population (4,5,30). Signs of bowel wall thickening with mucosal oedema appear on ultrasound as limited hypoechoic crescents, and colour Doppler is used for the detection of low flow in the involved part of the intestine (4,5,30). Another advantage of ultrasound is its ability to assess the amount of intra-abdominal fluid and to perform early detection of complications such as intussusception (4–6). Ultrasound has proved to be useful in the diagnostic procedure involving our patient with ileocaecocolic intussusception as well. The largest number of patients in our study had an ultrasound finding that showed no abnormalities, which corresponds to the results of other authors (4,6), followed by mesenteric lymphadenitis, which is also a common finding (4,5). Among the laboratory findings, it was observed that patients with gastrointestinal involvement had a statistically significantly higher number of leukocytes, which can be interpreted as a systemic response with leukocyte migration to the site of intestinal inflammation (7,18,28). Furthermore, significant differences were observed in terms of lower values in erythrocyte sedimentation rate and total protein in this group of patients. Lower total protein values have previously been described by Nagamori et al., and this finding could be associated with higher intestinal protein permeability due to intestinal vasculitis, but it could also be related to greater loss of protein and albumin through the kidneys, as most of these patients had nephritis (31). Although calprotectin is an important biomarker of inflammation, as it is released from neutrophils that migrate to the site of intestinal inflammation and then excreted in the stool (12,32), our study did not show a statistically significant difference in faecal calprotectin between the two groups (p = 0.377). The follow-up of patients with gastrointestinal symptoms lasted for six months and during that period all of them have recovered.

To conclude, most gastrointestinal symptoms in IgAV are self-limiting and often resolve spontaneously or with short-term drug use. Our study has confirmed that severe, life-threatening complications of IgAV are rare. However, the patients who developed gastrointestinal symptoms were also more prone to developing nephritis, the most important chronic complication of IgAV. Also, in our group of IgAV patients, patients with gastrointestinal symptoms were more often male, with a longer length of stay in the hospital, they were more often treated with glucocorticoids and antihypertensives, and had a higher incidence of relapse. This calls for caution and raises the question of the need for longer clinical follow-up of these patients to detect and ranog uočavanja komplikacija poput intususcepcije (4–6). I u slučaju našeg bolesnika s ileocekokoličnom invaginacijom crijeva ultrazvuk se pokazao korisnim u dijagnostici. Najveći broj bolesnika u našem istraživanju imao je uredan ultrazvučni nalaz, što odgovara i rezultatima drugih autora (4,6), potom mezenterijski limfadenitis koji je također čest nalaz (4,5). Među laboratorijskim nalazima uočeno je da su bolesnici sa zahvaćenim gastrointestinalnim sustavom imali statistički značajno veći broj leukocita, što se najvjerojatnije može protumačiti kao sustavni odgovor uz migraciju leukocita na mjesto crijevne upale (7,18,28). Nadalje, uočene su značajne razlike u smislu nižih vrijednosti u brzini sedimentacije eritrocita i ukupnih proteina u navedenoj skupini bolesnika. Snižene vrijednosti ukupnih proteina ranije su opisali Nagamori i sur., a taj bi se nalaz mogao povezati s većom propusnošću crijevne sluznice za bjelančevine uslijed vaskulitisa crijeva, ali možda i s većim gubitkom bjelančevina i albumina putem bubrega, s obzirom na to da su ti bolesnici češće imali nefritis (31). Iako je kalprotektin važan biomarker upale, budući da se oslobađa iz neutrofila koji migriraju na mjesto crijevne upale i potom izlučuje u stolici (12,32), u našem istraživanju nije zabilježena statistički značajna razlika u vrijednostima fekalnog kalprotektina između dviju skupina (p=0,377). Bolesnici s gastrointestinalnim simptomima praćeni su kroz šest mjeseci tijekom kojih je u svih došlo do oporavka.

Zaključno, većina gastrointestinalnih simptoma u IgAV-u jest samoograničavajuća pa često i spontano prestaje ili uz kratkotrajnu primjenu lijekova. Naše istraživanje je potvrdilo da su teške, po život opasne komplikacije IgAV-a rijetke. Međutim, bolesnici u kojih su se pojavili gastrointestinalni simptomi u konačnici su češće razvili nefritis, najvažniju kroničnu komplikaciju IgAV-a. Također, u našoj skupini bolesnika s IgAV-om bolesnici s gastrointestinalnim simptomima češće su bili muškog spola, imali su dulje trajanje hospitalizacije, češće su liječeni glukokortikoidima i antihipertenzivima te su imali veću pojavu relapsa. To nalaže oprez i otvara pitanje za potrebom duljega kliničkog praćenja ovih bolesnika kako bi se na vrijeme otkrile i počele liječiti moguće komplikacije bolesti.

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begin the treatment of the possible complications of the disease in time.

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