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RENAL INVOLVEMENT IN CHILDREN WITH SYSTEMIC VASCULITIS – A SINGLE TERTIARY CARE CENTER EXPERIENCE

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SUMMARY

Key words: renal injury, systemic vasculitis, ANCA.
Background. Renal involvement in children with systemic vasculitis is a common and often a severe complication. Kidney injury occurs in one third till one half of patients with confirmed IgA vasculitis and in 70% of patients with granulomatosis with polyangiitis (GPA) and in almost all confirmed patients with microscopic polyangiitis (MPA). *Aim of the study.* To analyze the association of renal injury with the clinical manifestations, degree of severity of the main diagnosis, specific and non-specific laboratory data, and options of treatment in patients with systemic vasculitis. *Method and materials.* We performed a retrospective review of pediatric patients who admitted to our center between 2018 and 2019, which were < 18 years on admission and had a diagnosis of vasculitis established. Patients demographics included: gender, age, median age at disease onset, disease duration, diagnosis and its degree of severity, laboratory tests and treatment options. *Results.* Baseline demographic data revealed the mean age for the general group of 10,53±1,34 years. Patients with renal involvement are older than those with no renal involvement. As well, disease duration was determined much longer in patients with renal involvement. Ratio distribution was different between subgroups – in patients with renal involvement, males were mostly affected with a ratio of 3:1. According to EULAR/ PRINTO/PRES 2010 diagnostic criteria our patients developed in 50% cases IgA Vasculitis. In about one third of cases were ANCA associated vasculitis. All ANCA associated vasculitis developed at presentation or in evolution of the disease, a renal injury. By comparison, renal involvement in IgA vasculitis is less common. The spectrum of clinical manifestations observed in our group of patients is wide, and is affecting a number of system and organs. The estimated GFR (according to Scwartz formula) was diminished in all patients with renal involvement. Immunological tests done within our patients revealed cANCA positive values in 62,5% cases of patients with renal involvement. *Conclusions.* Unfortunately, in children, the majority of studies have a limited follow-up. However, renal involvement is often associated with a worse long-term outcome.

РЕЗЮМЕ

ПОРАЖЕНИЕ ПОЧЕК У ДЕТЕЙ С СИСТЕМНЫМ ВАСКУЛИТОМ - ОПЫТ ЦЕНТРА ТРЕТИЧНОЙ ПОМОЩИ

Ключевые слова: повреждение почек, системный васкулит, АНКА.
Введение. Поражение почек у детей с системным васкулитом является распространенными часто тяжелым осложнением. Повреждение почек встречается у одной трети до половины пациентов с подтвержденным ИгА васкулитом и у 70% пациентов с гранулематозом с полиангиитом и почти у всех подтвержденных пациентов с микроскопическим полиангиитом.
Цель исследования. Проанализировать связь повреждения почек с клиническими проявлениями, степенью тяжести основного диагноза, специфическими и неспецифическими лабораторными данными и вариантами лечения у пациентов с системным васкулитом.
Материалы и метод. Мы провели ретроспективный обзор педиатрических пациентов, которые поступили в наш центр в период между 2018 и 2019 годами, которым было менее 18 лет при поступлении и был установлен диагноз васкулита. Данные пациентов включали: пол, возраст, средний возраст в начале заболевания, продолжительность заболевания, диагноз и степень его тяжести, лабораторные анализы и варианты лечения.
Результаты. Исходные демографические данные выявили средний возраст для общей группы 10,53±1,34 года. Пациенты с поражением почек старше, чем пациенты без поражения почек. Кроме того, продолжительность болезни была определена намного дольше у пациентов с поражением почек. Распределение соотношения было

различным в подгруппах - у пациентов с поражением почек мужчины чаще всего страдали с соотношением 3:1. Согласно диагностическим критериям EULAR / PRINTO / PRES 2010 у наших пациентов в 50% случаев развился ИгА васкулит. Приблизительно в одной трети случаев был ассоциированный цАНКА васкулит. Все ассоциированные цАНКА васкулиты развивались при появлении или в развитии заболевания, почечной патология. Для сравнения, поражение почек при ИгА васкулите встречается реже. Спектр клинических проявлений, наблюдаемых в нашей группе пациентов, широк и влияет на ряд систем и органов. Расчетная СКФ (согласно формуле Скарца) была снижена у всех пациентов с поражением почек. Иммунологические тесты, проведенные у наших пациентов, выявили положительные значения цАНКА в 62,5% случаев с поражением почек. *Выводы.* К сожалению, у детей большинство исследований имеют ограниченный период наблюдения. Однако поражение почек часто связано с худшим отдаленным исходом.

REZUMAT

AFECTAREA RENALĂ LA COPIII CU VASCULITE SISTEMICE – EXPERIENȚĂ LA NIVEL DE CENTRU DE NIVEL TERȚIAR

Cuvinte-cheie: afectare renală, vasculite sistemice, ANCA.

Actualitatea. Afectarea renală la copiii cu vasculite sistemice este o complicație frecventă și severă. Afectarea renală se atestă la o treime din pacienții cu vasculită IgA și la aproximativ 70% din pacienții cu granulomatoză cu poliangeită și la aproape toți pacienții cu poliangeită microscopică. *Scopul studiului.* A analiza impactul afectării renale asupra manifestărilor clinice, gradului de severitate, abnormalităților de laborator specifice și nonspecifice, precum și prezentarea opțiunilor de tratament la pacienții cu vasculite sistemice. *Material și metode.* Am efectuat o analiză retrospectivă a pacienților cu vârsta <18 ani internați în centrul nostru în perioada 2018-2019 cu diagnosticul confirmat de vasculită. Analiza statistică a datelor pacienților a inclus: sexul, vârsta, vârsta medie la debutul bolii, durata bolii, diagnosticul și gradul de severitate al ei, rezultatele analizelor de laborator și opțiunile de tratament. *Rezultate.* Analiza datelor demografice a relevant că vârsta medie pentru grupul general era de 10,53±1,34 ani. Pacienții cu afectare renală erau mai în vârstă decât cei fără afectare renală. De asemenea, durata bolii s-a dovedit a fi mai lungă la pacienții cu afectare renală. Distribuția pe sexe a fost diferită între cele două subgrupuri – printre pacienții cu afectare renală predominau băieții, în raport de 3:1. În baza criteriilor de diagnostic EULAR/PRINTO/PRES 2010, la pacienții din lotul general a fost confirmată vasculita IgA la 50% cazuri. În aproximativ 1/3 cazuri au fost confirmate vasculite ANCA asociate. Toate vasculitele ANCA asociate au dezvoltat – fie la debut, fie evolutiv, afectare renală, totodată patologia renală la pacienții cu vasculite IgA a fost mai rar depistată. Spectrul manifestărilor clinice observate în lotul general este variat, ele depistându-se în mai multe organe și sisteme. Rata de filtrare glomerulară estimată (în baza formulei Scwartz) era diminuată la toți pacienții cu patologie renală. Testele imunologice efectuate în lotul de pacienți cu afectare renală au depistat valori cANCA pozitive în 62,5% cazuri. *Concluzii.* După cum se știe, la copii, majoritatea studiilor au o continuitate limitată. Cu toate acestea, afectarea renală implică deseori un prognostic pe termen lung precar.

Background.

Renal involvement in children with systemic vasculitis is a common and often a severe complication. The long-term outcome of those confirmed diagnosis is dependent on the renal involvement.

One of the most common of systemic vasculitis in children is the IgA vasculitis (Henoch-Schoenlein purpura). Even if it is generally considered a self-limiting disease in the majority of cases, long-term prognosis depends on the timing and degree of severity of the renal involvement. Kidney injury occurs in one third till one half of patients with confirmed IgA vasculitis, mostly in those with a mild form with microscopic hematuria or/and mild proteinuria.[2,9]

More than that, renal involvement may develop during the acute or chronic phase, presenting as proteinuria and/or hematuria. Unfortunately, this condition sometimes can lead to systemic arterial hypertension and renal failure.[8]

Another category of systemic vasculitis is represented by anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis. In those cases, by comparison with IgA vasculitis, renal involvement is associated with significant morbidity and higher mortality rates. As incidence, renal disease can develop in approximatively 70% of patients with granulomatosis with polyangiitis (GPA) and in almost all confirmed patients with microscopic polyangiitis (MPA).[3,10]

Nowadays, the outcome of those cases is better than it was before. This fact is due to current therapies which had improved the renal function in the short term. However, medical evidence for long-term protection is currently missing.[7]

Aim.

The aim of our study was to analyze the association of renal injury with the clinical manifestations, degree of severity of the main diagnosis, specific and non-specific laboratory data, and options of treatment in patients with systemic vasculitis.

Methods and materials.

We performed a retrospective review of pediatric patients who admitted to our center between 2018 and 2019 and were < 18 years on admission and had a diagnosis of vasculitis established. Patients with systemic vasculitis, based on the EULAR/PRINTO/PRES (The European League Against Rheumatism/Pediatric Rheumatology International Trials Organization/Pediatric Rheumatology European Society) 2010 diagnostic criteria, were recruited from our data base registry.[1,11] Those who completed at least 6 months of follow up visits were recruited.

Patients demographics included: gender, age (years), median age at disease onset (years), disease duration (months), diagnosis and the degree of severity according to level of Birmingham score and vasculitis damage index (VDI). According to diagnosis, we grouped our patients in to three categories: IgA vasculitis, ANCA associated vasculitis or unspecified forms. Further those ANCA associated vasculitis will be divided in to granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA).

From clinical course we analyzed our group of patients on the presence and severity of skin involvement, the presence of peripheric edema and macroscopic hematuria or other dysuric symptoms. In all patients was monitored the blood pressure and interpreted according to the percentile age and height specific. Values higher than the 95th percentile were considered values of increased blood pressure systolic and/or diastolic.

We divided the main group of patients into two subgroups according to the renal involvement– with renal involvement (Group A) or without renal involvement (Group B). The last one was established based on the presence of the following laboratory data – hematuria, proteinuria, serum creatinine level and estimated glomerular filtration rate (GFR). Hematuria was defined as greater than 10 red blood cells per high-power field. Proteinuria was defined as greater than 0,033 g/L of protein in the urine sample or 24hour urine protein higher than 1 g/L. Abnormal renal function was defined according to serum creatinine level and estimated GFR. It was considered positive a rise in creatinine >30% from baseline, or an estimated GFR of <90 ml/minute/1,73 m^2. None of our cases did not been attributable to other causes of kidney injury, including drug toxicity or dehydration. In all cases, GFR's were calculated using the revised Schwartz formula.

Other analyzed laboratory data included: erythrocyte sedimentation rate (mm/h), C reactive protein (CRP, in mg/L), fibrinogen level (g/L), serum creatinine and urea level. For immunologic tests we looked for circulating immune complements, complement C3and C4, antinuclear antibody level on hep2 substrate, as well as screening and confirmation test for systemic vasculitis (cANCA, pANCA, MPO, PR3)

The degree of severity was assessed according to the Birmingham Vasculits Activity Score (BVAS) and the Vasculitis Damage Index (VDI). Both of them are a validated and standardized tool assessment in adults. [13] Due to the missing validated tool to assess disease damage in children with vasculitis, we used both BVAS and VDI.

The plan of treatment was analyzed for both periods: induction of remission and maintaining period.

Informed consent was not required because the study was retrospective.

Statistical analyses had been done in MO Excel 2016 and 26th edition SPSS. Nominal variables are presented as frequencies. Ordinal variables were described by descriptive analysis. The final report included mean value and the standard error, minimum and maximum values and the confidence level.

Results and discussions.

The data analyze of our group of patients revealed some information for clinical and laboratory associations of renal involvement in pediatric systemic vasculitis. Some of it correspond to the known information about this disease published in the literature. However, there are some differences. In our study, however, several limitations exist. Firstly, it should be noted that this study used a relatively small sample size. Secondly, a constraint of our study is missing data for kidney biopsy.

The analyze of baseline demographic data revealed the mean age for the general group of 10.53±1.34 years. A difference was noticed between subgroups. Those patients with renal involvement (Group A) were older than those with no renal involvement (Group B), 11.15±1.76ys and, respectively, 9.7±2.21ys. In Figure 1 and 2 are represented frequencies for groups of age, as well the distribution according to gender and age. Similar, data from literature refers to the age older than 8 years as a risk factor for the development of nephritis. [4,10]

Statistical analyze of the mean age at disease onset, revealed no differencebetween subgroups. The general groups had a mean age at disease onset of 9.67±1.24ys, with a reference between 2.14ys till 16.61ys. Disease duration (in months) was determined much longer in patients from group A, 23.02±8.79mo versus 4.39±2.14mo.

Ratio distribution, male:female was 1.33:1 in the general group. However, it was different between subgroups – in patients with renal involvement, males were mostly affected with a ratio of 3:1. Similar data was presented in a previous meta-analysis, which suggested that boys are at higher risk for renal involvement than girls. Despite this, there some studies which showed no association between gender and outcome. If to discuss about vasculitis subtypes, then in patients with IgA vasculitis, most studies reported no association between gender and long-term outcomes of renal involvement. [6,10]

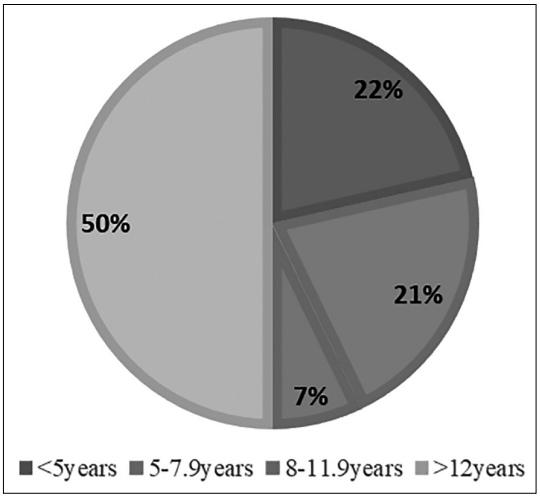

Fig. 1. Age groups distribution

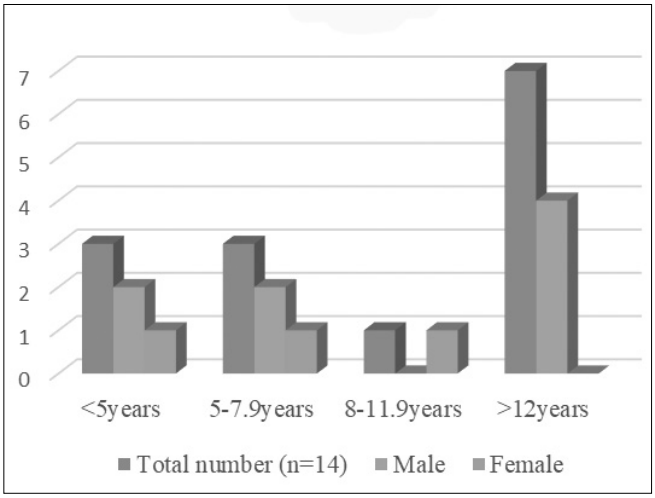

Fig. 2. Distribution according gender and age

Table 1. Demographic data for general group, subgroups A and B.

	General group (n=14)	***Subgroup A Renal involvement (n=8)***	***Subgroup B No renal involvement (n=6)***
Demographics			
Gender ratio (M:F)	1.33:1	3:1	1:2
Age (years)	10.53±1.34 [3.58;17.19]	11.15±1.76 [3.58; 17.19]	9.7±2.21 [4.28; 15.93]
Mean age at disease onset (years)	9.67±1.24 [2.14;16.61]	9.88±1.64 [2.14; 16.61]	9.39±2.09 [4.26; 15.25]
Disease duration (months)	15.04±5.57 [0.23;67]	23.02±8.79 [0.23; 67]	4.39±2.14 [0.23; 12]

All detailed demographic data for general group, and subgroups A and B are presented in table 1.

According to EULAR/PRINTO/PRES 2010 diagnostic criteria our patients developed in 50% cases IgA Vasculitis. In about one third of cases were ANCA associated vasculitis, and in two cases clinical and laboratory data were insufficient to specify the clinical form of systemic vasculitis. The missing opportunities to undergo kidney biopsy classified them as unspecific form of systemic vasculitis. From those ANCA associated vasculitis 3 of them were MPA and the rest of two were GPA. To underline, that all ANCA associated vasculitis developed at presentation or in evolution of the disease, a renal injury. By comparison, renal involvement in IgA vasculitis is less common (table 2). The degree of severity was assessed based on two tools: BVAS and VDI. In case of BVAS a higher score than 9 was calculated in subgroup A, children with renal involvement, higher values (up to 23) where determined in patients with GPA and MPA. The mean value for BVAS in subgroup B was 3±0,77 by comparison to 9,87±3,10 in subgroup A. Similar, VDI higher values

Table 2. Diagnosis, subtypes and degree of severity

		General group (n=14)	***Subgroup A Renal involvement (n=8)***	***Subgroup B No renal involvement (n=6)***
Diagnosis				
Diagnosis	IgA vasculitis	7/14 cases 50%	2/8 cases 25%	5/6 cases
	ANCA[1]+ vasculitis	5/14 cases 35.71%	5/8 cases 62.5%	-
	Unspecified	2/14 cases 14.28%	1/8 cases 12.5 %	1/6 case
BVAS[2]		6.64±2.0 [1;23]	9.87±3.10 [1; 23]	3±0.77 [1; 6]
VDI[3]		4.71±1.83 [0;21]	5.87±2.2 [1; 16]	1±0.25 [0; 2]

[1]Anti-neutrophil cytoplasm antibody - associated vasculitis; [2]Birmingham Vasculitis Activity Score; [3]Vasculitis Damage Index.

were confirmed just in patients from group A, with a mean value of 5,87±2,2. According to literature data, higher values than 9 for BVAS and, respectively, 5 for VDI are considered risk factors for disease evolution and outcome.[1,4,13]

The spectrum of clinical manifestations observed in our group of patients is wide, and is affecting a number of system and organs. Our patients were from cutaneous involvement, musculoskeletal, ENT, renal, cardiovascular, inclusively neurological and pulmonary involvement. Similar to literature date, almost all our patients reported constitutional symptoms of malaise, fever and/or weight loss. Skin involvement was confirmed in 78,57% cases and included palpable purpura, livedo and/or petechial rash. Rarely, were noticed subcutaneous nodule. Fig. 3 represent a case-serie with mucocutaneous elements from our patients. According to some studies, the degree of severity of skin involvement could be a marker for the renal involvement and for a worse-outcome.

Many studies suggest than age at onset of more than 7 years old, severe abdominal symptoms, persistent purpuric lesions are associated with an increased risk of nephritis. [2, 10, 12]

Regarding renal injury, our patients did not complaint for dysuric symptoms. One third of them complaint for macroscopic hematuria. The study presented by Schinzel et al.(2019), also, identified macroscopic hematuria in 20% cases. [8] In the same way, the presence of peripherical edema was around 35% cases, with no difference between subgroup A and B. The difference between subgroups was made by high values of systolic and diastolic blood pressure. In almost half of the cases were determined systolic blood pressure higher than the 95th percentile according to gender and height. However, in subgroup A its incidence was of 62,5% by comparison to 16.6% in children with no renal involvement. Values for diastolic blood pressure above the 95th percentile was exclusively in children with renal involvement (table 3).

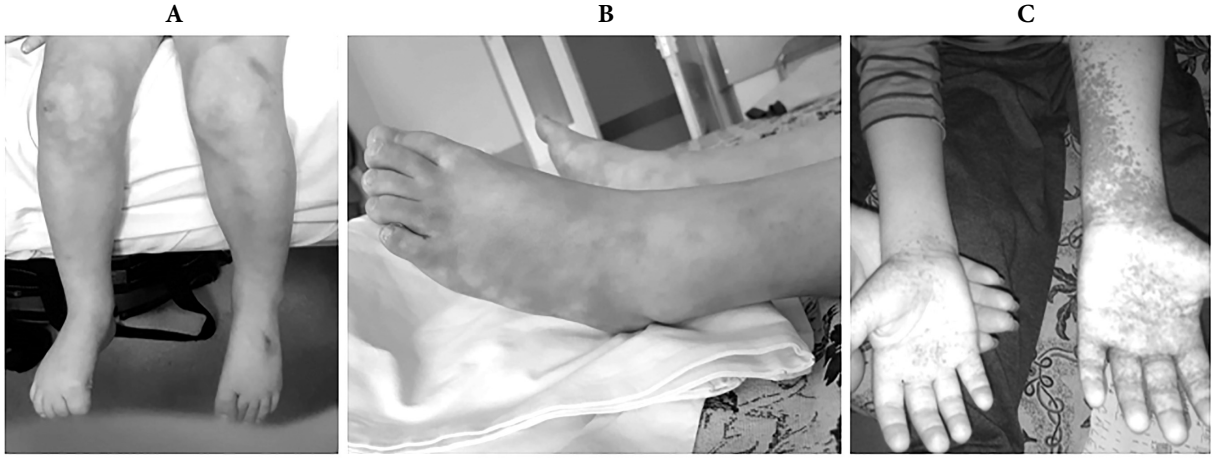

Fig. 3. Cutaneous manifestations in children with systemic vasculitis

Our presented data correspond to ANCA-associated vasculitis tree of knowledge, where kidney involvement is almost equal in both categories – MPA and GPA. [5]

Table 4 shows statistical data for the laboratory tests in general groups and both subgroups. Further, we will highlight the main differences observed. In patients with renal involvement serum creatinine level was higher than the age-specific reference range in 87,5% cases by comparison to 33,3% cases in the second subgroup. Secondly, the estimated GFR (according to Scwartz formula) was diminished in all patients from subgroup A with a mean value of 60,93±3,36 ml/minute/1,73 m^2 with a distribution from 48,14 to 75,59. On the other side, diminished eGFR values were in one third of patient, with mean values much greater than the previous values

Table 3. Selection of clinical manifestations and its statistical analysis

	General group (n=14)	***Subgroup A Renal involvement (n=8)***	***Subgroup B No renal involvement (n=6)***
Clinical manifestations			
Skin involvement	78.57%	6/8 cases; 75%	5/6 cases;
Peripherical edema	35.71%	25%	33.3%
Systolic blood pressure (>95 percentile)	42.85%	62.5%	16.6%
Dyastolic blood pressure (>95 percentile)	21.42%	37.5%	-
Macroscopic hematuria	28.57%	37.5%	-

(data available in table 4). According to data literature, lower level of eGFR is a risk factor for progressing to unfavorable outcomes in pediatric patiens with systemic vasculitis and its subtypes – IgA vasculitis, MPA, GPA or other specific conditions. [2,3,7]

Very important to focus that, the one laboratory test that is highly useful for staging organ involvement is urinalysis. Consequently, the presence of red blood cell casts is regarded as having high specificity (although low sensitivity) for nephritis. The presence of significant proteinuria is an important marker for staging and prognosis in pediatric patients with systemic vasculitis and is often used to make decisions regarding treatment.

Table 4. Selection of clinical manifestations and its statistical analysis

	General group (n=14)	***Subgroup A Renal involvement (n=8)***	***Subgroup B No renal involvement (n=6)***
Laboratory investigations			
ESR (mm/hr)	Elevated in 50% cases 14.28±2.6 [2; 36]	Elevated in 50% cases 14.25±3.91 [4; 36]	Elevated in 50% cases 14.33±3.55 [2; 24]
CRP (mg/L)	Elevated in 21.42% cases 40.5 [6; 96]	Elevated in 12.5% cases [0; 48]	Elevated in 33,33% cases [12; 96]
Fibrinogen	2.9±0.2 [2; 4.9]	2.97 ± 0.36 [2; 4.88]	2.9±0.34 [1.97; 4.47]
Serum creatinine (mcmol/l)	Elevated in 64.28% cases 74.78±5.86 [40; 117]	Elevated in 87.5% cases 85.5±6.41 [58; 117]	Elevated in 33.3% cases 60.5±7.75 [40; 81]
GFR (according to Scwartz formula)	Diminished in 85.71% cases 70.92±4.08 [48.14; 99.73]	Diminished in 100% cases 60.93±3.36 [48.14; 75.59]	Diminished in 33.3% cases 84.25±4.24 [75.94; 99.73]
Microscopic hematuria	Present in 71.42% cases	Present in 37,5% cases	-
Proteinuria	21,42% cases	37.5% cases	-
24 hour urine protein >1 g/d	1/14 cases	1/8 case	-
cANCA	5/14 cases 35.71%	5/8 cases; 62.5% cases	-
pANCA	1/14 cases; 7.14% cases	1/8 case	-
MPO	4/14 cases; 28.57% cases [14; 28]	4/8 cases; 50% cases	-
PR3	2/14 cases; 14.28% cases [18; 108]	2/8 cases; 25% cases	-

[6] There are some limits regarding proteinuria as tool of comparison between different studies. [9] This fact is due to different data presentation and measurement method of proteinuria. However, once kidney damage has occurred, proteinuria, hematuria, and even red blood cell casts may persist without evidence of progressive kidney disease, so the high sensitivity and specificity of different aspects of urinalysis are apparent only during the first episode of nephritis.[6]

Interestingly, we did not find no difference between ESR, CRP and fibrinogen level between study groups. Similar findings are revealed in other studies. One possible explanation is that those serum markers are more easily affected by other factors (such as potential infection).[10] Immunological tests done within our patients revealed cANCA positive values in 62,5% cases of patients with renal involvement. Half of them was with positive values of MPO antibodies and just 25% determined positive PR3 antibodies. According to literature date PR3-ANCA is associated with significantly increased relapse rate. [5]

The associations of baseline demographic and clinical characteristics (e.g., age, gender, and hypertension) and laboratory predictors (GFR, serum creatinine, and level of proteinuria) of study subjects with prognosis in patients with renal involvement were analyzed to assess risk factors for unfavorable outcomes. However, there is a need for better biomarkers in vasculitis: for diagnosis, staging, assessment of current disease activity, and prognosis.[6]

Currently, the only practical tool for estimating the renal prognosis of ANCA-GN is the histopathologic classification proposed in 2010. [11] Unfortunately, in clinical work, not all patients are able to undergo kidney biopsy. [10] However, a kidney biopsy remains a gold standard for evaluating the severity of renal vasculitis and its associated prognosis. [2, 7]

The majority of our patients received intravenous or oral prednisolone. In confirmed nephritis also, some of them received cyclophosphamide every two weeks (Pulse Cyclophosphamide) according to body

weight. Oral corticosteroid+ Cyclophosphamide or corticosteroid+azathioprine was administered for more than 1 year for maintenance therapy. Each regimen of treatment was established by individualized approach according to EULAR and/or KDIGO guidelines. According some studies, in the treatment of ANCA-associated vasculitis with renal involvement, prednisolone has been more recommended due to its superiority to metilprednisolone. [10]

It is important to underline that EULAR/ERA-EDTA (European League Against Rheumatism/ European Renal Association—European Dialysis and Transplant Association recommend treatment with a combination of glucocorticoids and either cyclophosphamide or rituximab. Rituximab is preferred as a first line remission induction therapy for patients in whom CYC is contraindicated or presents any risks. [11] One of our patient develop a similar situation, due to which received Rituximab treatment once per week during 4 weeks consequently.

In particular, EULAR/ERA-EDTA guidelines recommend switching from rituximab to cyclophosphamide and vice versa for relapsing ANCA associated vasculitis. In those who continue to have persistent active disease, intravenous immunoglobulin may be used as an adjunctive therapy.[7,11]

Conclusions.

The collaborative efforts among pediatric rheumatologist have helped in recognizing common clinical features and treatment choices in these conditions. Unfortunately, in children, the majority of studies have a limited follow-up. However, renal involvement is often associated with a worse long-term outcome. Early renal biopsy should be considered in patients with renal involvement.While modern immunosuppressive regimens have dramatically improved the prognosis for systematic, the associated disease and therapy-related morbidity and mortality remain high.

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