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ORIGINAL ARTICLE

Does age at disease onset affect the clinical presentation and outcome in children with immunoglobulin A vasculitis?

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ABSTRACT

Objectives: The study aimed to determine whether there is a relationship between the age at diagnosis and the clinical, laboratory, and prognostic features in pediatric immunoglobulin A vasculitis (IgAV) patients.

Patients and methods: In this study, 539 pediatric IgAV patients (298 males, 241 females; mean age: 7.74±3.36 years; range, 1 to 17.8 years) were retrospectively evaluated between January 2005 and July 2020. The relationship between clinical findings and age at diagnosis was analyzed by univariate logistic regression analysis. Factors associated with renal involvement, steroid-dependent or refractory disease, and recurrence were examined.

Results: The median age of diagnosis was 7.1 (1-17.8) years in all patients. At the time of admission, purpura, abdominal pain, and arthritis were the most common clinical findings. At the time of diagnosis, there was a positive association between age and purpura and an inverse association with the presence of arthritis. There were associations between renal involvement and age at diagnosis (odds ratio=1.22, 95% confidence interval 1.13-1.31, p<0.001), follow-up time (p<0.001), no history of previous infection (p<0.001), and presence of gastrointestinal (GI) involvement (p=0.003). Significant relationships were found between the age at diagnosis, follow-up time, GI involvement, renal involvement, scrotal involvement, the C-reactive protein value at the time of diagnosis, and the presence of steroid-dependent disease. An association was found between recurrence and GI involvement. All refractory patients had renal involvement. Age at diagnosis (p<0.001) and follow-up time (p<0.001) was found to be associated with refractory disease.

Conclusion: Age at diagnosis and follow-up time may be associated with renal involvement and refractory and steroid-dependent disease in IgAV. In addition, there may be a relationship between steroid-dependent disease and renal, GI, and scrotal involvement and between GI involvement and recurrence.

Keywords: Age at diagnosis, recurrence, refractory disease, steroid-dependent disease.

Immunoglobulin A vasculitis (IgAV) is a leukocytoclastic vasculitis affecting small vessels characterized by the accumulation of immunoglobulin A in the vessel wall. Nonthrombocytopenic purpura, abdominal pain, arthritis/arthralgia, and glomerulonephritis are common clinical findings.[1] Its incidence is 6-22/100,000 person-years, and it is the most common vasculitis in childhood.[2-5] It can be seen in children at any age but is most common between the ages of four to six. The prevalence is higher in males.[3,6] Generally, the clinic is self-limiting, but in severe cases, corticosteroid and immunosuppressive therapy may be required.[7]

There are clinical differences between pediatric and adult IgAV cases. Male sex, renal involvement, and renal failure are more common in adult patients. While the disease is usually self-limiting in childhood, it can be more severe and have a worse prognosis in adulthood.[8-13] The frequency of renal involvement increases with age in children as well.[14] There is a limited number of studies evaluating a relationship between the age of disease onset and clinical course in pediatric IgAV.[15] Therefore, this study primarily aimed to determine the relationship between the age at diagnosis and the clinical features as well as outcomes in IgAV patients and, secondarily, the effect of other demographic and clinical findings on the outcomes of the disease.

PATIENTS AND METHODS

In this study, 539 IgAV patients (298 males, 241 females; mean age: 7.74±3.36 years; range, 1 to 17.8 years) who applied to the outpatient clinic of Gazi University Faculty of Medicine, Department of Pediatric Rheumatology between January 2005 and July 2020 were retrospectively analyzed. All patients were younger than 18 years of age at the time of diagnosis and met EULAR (European League Against Rheumatism)/PRINTO (Paediatric Rheumatology International Trials Organisation)/PRES (Paediatric Rheumatology European Society) Henoch-Schönlein purpura classification criteria.[16]

Age, sex, clinical and laboratory findings, and treatments were retrieved from the file records of the patients. Age at diagnosis was determined as the age at which the patient met the EULAR/PRINTO/PRES Henoch-Schönlein purpura classification criteria. Gastrointestinal (GI) system involvement was defined as the presence of invagination, GI bleeding, or sudden onset of abdominal pain. Renal involvement was defined as the presence of proteinuria (proteinuria >4 mg/m^2/h) and/or hematuria (red cell casts, red blood cell count >5 at highest magnification, or hematuria of +2 or higher in dipstick). Scrotal involvement was defined as the presence of testicular pain, swelling, or redness in addition to the presence of epididymitis or scrotal effusion in ultrasonography. Requirement of corticosteroid use for six weeks or longer at any stage of the disease was defined as steroid-dependent disease. Recurrent disease was defined as the reemergence of IgAV clinical findings at least three months after complete remission was achieved and all medical treatment was discontinued. The three-month timeline was determined based on previous epidemiological studies of IgAV.[17-19] The refractory disease was defined as the inability to achieve complete remission despite six months of treatment. Complete remission was defined as the resolution of purpura, disappearance of proteinuria and hematuria with normal renal functions, relief of GI symptoms and signs, arthritis/arthralgia, and scrotal findings.

Statistical analysis

Data were analyzed with IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Categorical data were presented by frequency and percentage. Continuous data were expressed as mean ± standard deviation (SD) or median (minimum-maximum). The relationship between clinical findings and age at diagnosis was analyzed by univariate logistic regression analysis. First, univariate logistic regression analysis was performed to identify factors associated with renal involvement, GI involvement, and steroid-dependent, recurrent, or refractory disease. Variables that have $p<0.250$ in the univariate logistic regression analysis were put into multivariable logistic regression analysis, and modeling was performed. The odds ratios (OR) with 95% confidence intervals were calculated. The Hosmer-Lemeshow test was used to assess goodness of fit. A p-value <0.05 was considered statistically significant.

RESULTS

The median age at the diagnosis of the patients was 7.1 (1-17.8) years (Figure 1). The median follow-up was 0.64 (0.1-13.7) years. There was a history of infection in 248 (46%) of the patients. At the time of diagnosis, the median C-reactive protein (CRP) was 6.9 (0.6-318) mg/L, and erythrocyte sedimentation rate (ESR) was 23 (1-125) mm/h. Mediterranean fever gene analysis was performed in 140 patients, and 45% of them had various mutations.

The most common complaints at presentation were purpura (66.8%), abdominal pain (14.3%), and arthritis (9.8%). There was GI involvement in 56%, renal involvement in 19.5%, and scrotal involvement in 16.8% of the patients (Table 1). When the relationship between age at diagnosis and clinical findings was evaluated with univariate logistic regression analysis, it was observed that there was a positive association between age at diagnosis and purpura at the time of diagnosis and an inverse association with the presence of arthritis at the time of diagnosis and scrotal pain (Table 1).

There was recurrent disease in 6.9%, refractory disease in 5%, and steroid-dependent disease in 13.4% of the patients (Table 2). Univariate and multivariable logistic regression analyses were performed to investigate the factors associated with renal involvement, steroid-dependent disease,

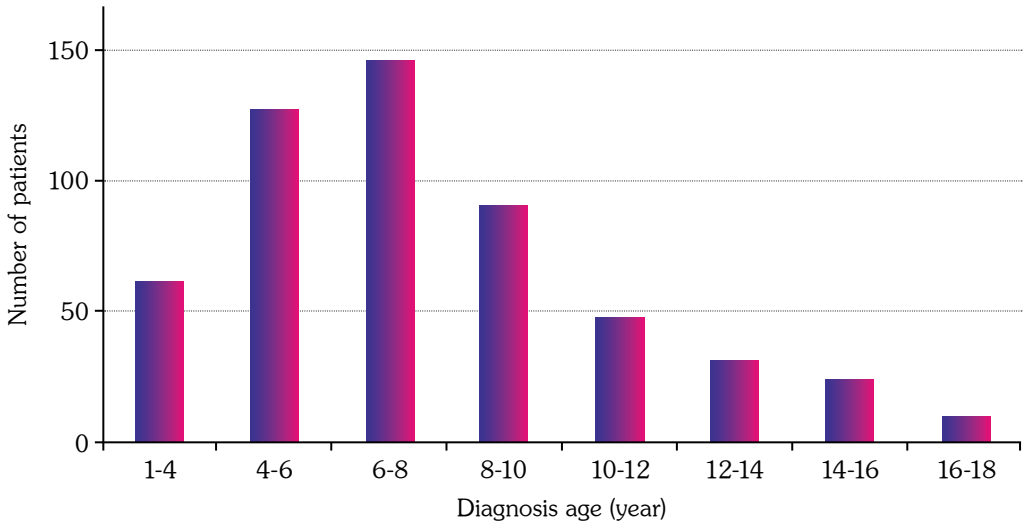

Figure 1. Distribution of patients by age at diagnosis.

recurrence, and refractory disease. There were associations between renal involvement and age at diagnosis (OR=1.22, 95% confidence interval [CI]: 1.13-1.31, p<0.001), follow-up time (OR=1.44, 95% CI: 1.30-1.60, p<0.001), no history of previous infection (p<0.001), and presence of GI involvement (OR=2.2, 95% CI: 1.31-3.71, p=0.003) (Table 3).

In the multivariable analysis, significant relationships were found between the age at

Table 1. Clinical characteristics of the patients and examination of the relationship between clinical findings and age at diagnosis with univariate analyzes (n=539)

			Age at diagnosis, year Univariate analysis with clinical findings	
	n	%†	OR	95% CI
First symptom				
Purpura	360	66.8	1.06	1.00-1.12*
Arthritis	53	9.8	0.85	0.76-0.94*
Arthralgia (without arthritis)	24	4.5	0.99	0.87-1.12
Fever	13	2.4	0.88	0.72-1.07
Abdominal pain	77	14.3	1.03	0.96-1.10
Vomiting	2	0.4	1.33	0.93-1.92
Diarrhea	1	0.2	0.84	0.40-1.75
Scrotal pain	1/298‡	0.3	0.62	0.24-1.59
Subcutaneous edema	8	1.5	0.90	0.70-1.14
Cumulative symptoms				
Purpura	539	100	-	-
Arthritis	318	59	0.96	0.91-1.01
Fever	77	14.3	0.95	0.88-1.03
Abdominal pain	290	53.8	0.97	0.92-1.02
Vomiting	57	10.6	0.95	0.87-1.04
Diarrhea	46	8.5	1.02	0.93-1.11
Scrotal pain	50/298‡	16.8	0.85	0.76-0.94*
Subcutaneous edema	29	5.4	0.97	0.86-1.09
Organ/system involvement				
GIS involvement	302	56	0.96	0.91-1.01
Renal involvement	105	19.5	1.13	1.07-1.20*
Scrotal involvement	50/298‡	16.8	0.84	0.76-0.94*

OR: Odds ratio; CI: Confidence interval; GIS: Gastrointestinal system; * p<0.001; † Data presented as frequency and percentage; ‡ Only male patients' data are presented.

Table 2. Outcome and medication information of all patients

	n	%
Outcomes†		
Recurrent disease	37	6.9
Refractor disease	27	5
Steroid-dependent disease	72	13.4
Medication†		
Ibuprofen	363	67.3
Glucocorticoid	181	33.6
Cyclophosphamide	11	2
Azathioprine	1	0.2
Cyclosporine	8	1.5
Colchicine	22	4.1
Enalapril	47	8.7

† Data presented as frequency and percentage.

diagnosis, follow-up time, GI involvement, renal involvement, scrotal involvement, the CRP value at the time of diagnosis, and the presence of steroid-dependent disease (Table 4). An association was only found between recurrence and the presence of GI involvement (OR=3.88, 95% CI: 1.28-11.72, p=0.016 in Model 1, and OR=2.65, 95% CI: 1.17-6, p=0.019 in Model 2; Table 5).

Since renal involvement was observed in all patients with refractory disease, it was not included in multivariable analyses for refractory disease. Multivariable logistic regression analysis was performed with the variables of the age of diagnosis, follow-up time, the presence of a previous infection, and GI involvement. In this

Table 3. Factors associated with renal involvement

	Univariate analysis			Multivariable analysis*		
	OR	95% CI	*p*	OR	95% CI	*p*
Diagnosis age (year)	1.13	1.07-1.20	<0.001	1.22	1.13-1.31	**<0.001**
Follow-up (year)	1.37	1.25-1.51	<0.001	1.44	1.30-160	**<0.001**
Sex						
Male	0.95	0.62-1.46	0.818	-	-	-
Previous infection	0.37	0.23-0.60	<0.001	0.38	0.23-0.64	**<0.001**
Arthritis	0.87	0.56-1.33	0.515	-	-	-
GIS involvement	2.41	1.51-3.85	<0.001	2.20	1.31-3.71	**0.003**
Scrotal involvement	0.77	0.34-1.75	0.539	-	-	-
C-reactive protein	1.00	0.99-1.01	0.682	-	-	-

OR: Odds ratio; CI: Confidence interval; GIS: Gastrointestinal system; * Hosmer and Lemeshow Test, Chi-square 11.799 p=0.160; Statistically significant results are indicated by bold-face type.

Table 4. Factors associated with steroid-dependent disease

	Univariate analysis			Multivariable analysis Model 1*			Multivariable analysis Model 2**		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Diagnosis age (year)	1.12	1.04-1.20	**0.002**	1.16	1.03-1.31	**0.017**	1.15	1.05-1.26	**0.004**
Follow-up (year)	1.28	1.16-1.41	**<0.001**	1.27	1.07-1.52	**0.008**	1.19	1.05-1.34	**0.006**
Sex									
Male	1.23	0.74-2.04	0.417	-	-	-	-	-	-
Previous infection	0.50	0.30-0.86	**0.011**	1.26	0.56-2.87	0.576	0.80	0.41-1.55	0.801
Arthritis	1.03	0.62-1.72	0.893	-	-	-	-	-	-
GIS involvement	7.70	3.61-16.41	**<0.001**	5.64	1.91-16.6	**0.002**	5.85	2.54-13.50	**<0.001**
Renal involvement	9.69	5.64-16.65	**<0.001**	5.04	2.09-12.11	**<0.001**	5.85	3.05-11.23	**<0.001**
Scrotal involvement	2.55	1.22-5.34	**0.013**	4.01	1.54-10.47	**0.004**	-	-	-
C-reactive protein	1.01	1.00-1.02	**0.017**	1.01	0.99-1.03	0.201	1.01	1.00-1.02	**0.044**

OR: Odds ratio; CI: Confidence interval; GIS: Gastrointestinal system; * Hosmer and Lemeshow Test, Chi-square 9.170 p=0.328 for Model 1; ** Hosmer and Lemeshow Test Chi-square 11.35 p=0.182 for Model 2. Since scrotal involvement was evaluated only in male patients, scrotal involvement was excluded in Model 2 in order not to exclude female patients as well. Statistically significant results are indicated by bold-face type.

Table 5. Factors associated with recurrence

	Univariate analysis			Multivariable analysis Model 1*			Multivariable analysis Model 2**		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Diagnosis age (year)	0.95	0.86-1.06	0.378	-	-	-	-	-	-
Follow-up (year)	1.15	1.01-1.30	**0.028**	1.10	0.92-1.31	0.281	1.10	0.96-1.26	0.152
Sex Male	2.00	0.97-4.13	0.062	-	-	-	2.01	0.96-4.22	0.063
Previous infection	0.89	0.45-1.74	0.726	-	-	-	-	-	-
Arthritis	0.72	0.37-1.40	0.329	-	-	-	-	-	-
GIS involvement	3.04	1.36-6.78	**0.007**	3.88	1.28-11.72	**0.016**	2.65	1.17-6	**0.019**
Renal involvement	2.11	1.02-4.35	**0.043**	1.25	0.45-3.44	0.663	2.01	0.96-4.22	0.282
Scrotal involvement	2.43	0.99-5.96	0.052	2.324	0.89-5.63	0.086	-	-	-
C-reactive protein	0.99	0.98-1.01	0.448	-	-	-	-	-	-

OR: Odds ratio; CI: Confidence interval; GIS: Gastrointestinal system; * Hosmer and Lemeshow Test Chi-square 4.089 p=0.849 for Model 1. Since scrotal involvement is only seen in males, the female gender effect was not evaluated in Model 1; ** Hosmer and Lemeshow Test Chi-square 10.972 p=0.203 for Model 2. Since scrotal involvement was evaluated only in male patients, scrotal involvement was excluded in Model 2 in order not to exclude female patients as well. Statistically significant results are indicated by bold-face type.

Table 6. Factors associated with refractory disease**

	Univariate analysis			Multivariable analysis*		
	OR	95% CI	*p*	OR	95% CI	*p*
Diagnosis age (year)	1.14	1.02-1.26	0.016	1.14	1.10-1.41	**<0.001**
Follow-up (year)	1.39	1.23-1.57	<0.001	1.48	1.28-1.70	**<0.001**
Sex Male	1.01	0.46-2.20	0.977	-	-	-
Previous infection	0.57	0.25-1.29	0.180	0.64	0.27-1.53	0.314
Arthritis	1.41	0.62-3.21	0.408	-	-	-
GIS involvement	2.33	0.97-5.61	0.059	1.92	0.76-4.85	0.167
Scrotal involvement	0.34	0.04-2.65	0.304	-	-	-
C-reactive protein	1.01	0.99-1.01	0.687	-	-	-

OR: Odds ratio; CI: Confidence interval; GIS: Gastrointestinal system; * Hosmer and Lemeshow Chi-square 2.600 p=0.957; ** All refractory patients have renal involvement. Statistically significant results are indicated by bold-face type.

model, age at diagnosis (OR=1.14, 95% CI: 1.10-1.41, p<0.001) and follow-up time (OR=1.48, 95% CI: 1.28-1.70, p<0.001) were found to be associated with refractory disease (Table 6).

DISCUSSION

Many studies have been conducted examining the clinical findings and outcomes of adult- and pediatric-onset IgAV patients, and similarities and differences have been tried to be revealed.[10-12,20-22] Male sex is common in both groups.[10,21,23,24] Abdominal pain and joint involvement as initial symptoms are less frequent in adults.[25] Renal involvement, signs of renal failure, and relapse are more common in adults than in children, while the disease tends to be self-limiting in pediatric patients.[10,21-23] The frequency of GI involvement is generally similar in adult and pediatric IgAV patients.[8-12] The number of studies investigating the effect of age at disease onset on disease

course and prognosis in pediatric IgAV cases is very low, except for renal involvement.[14,15,26] Therefore, in this study, we investigated the effect of age at disease onset on clinical findings and disease course. In univariate analyses, we found a positive relationship between age at diagnosis and the purpura (as the initial symptom) and an inverse relationship between arthritis (as the initial symptom) and scrotal involvement. In multivariable analyses, we demonstrated an association between increasing age at diagnosis and renal involvement, steroid-dependent disease, and refractory disease.

In childhood, purpura may occur in childhood vasculitis, infections, neonatal purpura fulminans, thrombocytopenia, and hemostasis disorders.[27,28] Palpable purpura is the most common, pathognomonic, and mandatory criterion for the diagnosis of IgAV.[8,14,16] It has been more frequently observed as an initial complaint in adults compared to children.[20] Development of arthritis is generally more common in children than adults during clinical course; however, similar rates have also been reported.[8-12,20] While there are studies reporting that the incidence of arthritis increases as the age of onset decreases in pediatric IgAV patients, other studies showing that there is no relationship between age and arthritis.[14,15,26] In the early period, the inability of children to describe their pain may have caused this situation.

The incidence of IgAV nephritis varies between 21 and 54%. It manifests with hematuria and proteinuria and is mostly in remission with treatment.[2,8,9,11,14,26] In our cohort, IgAV nephritis was detected in 19.5% of patients. It was slightly rarer compared to previous studies. Differences in the definition of renal involvement in studies may have caused this.[14,15,29,30] In a meta-analysis evaluating risk factors for renal involvement in IgAV, >10 years (age), male sex, leukocytosis, thrombocytosis, GI involvement, increased antistreptolysin O, low C3, and persistent purpura were found to be associated with renal involvement.[29] Studies comparing adult and pediatric IgAV patients have also shown that renal involvement occurs more frequently in adults.[21,24] In our data, there was a relationship between renal involvement and age at diagnosis, follow-up duration, and GI involvement. At the same time, the absence of a previous infection seemed to be an associated factor.

Scrotal involvement can be seen in 2 to 38% of IgAV patients. Patients may present with testicular pain, swelling, and redness.[31-33] In our series, scrotal involvement was found in 16.8% of male patients. We evaluated the characteristics of IgAV patients with scrotal involvement in a previous study. In the study, we emphasized that there is a relationship between decreasing age at diagnosis and scrotal involvement.[34] Therefore, we did not analyze scrotal involvement in detail in the current study.

Corticosteroid use is required in 20 to 73% of IgAV patients.[8,19,35] The shortest possible duration should be preferred to avoid side effects due to prolonged use of corticosteroids.[36] Therefore, it is important to decide which patients need long-term corticosteroid use. In this study, we defined steroid-dependent disease as the need for using corticosteroids for more than six weeks. In the current study, when all patients were evaluated (Table 4, Model 2), there was a relationship between steroid-dependent disease and an increase in age at diagnosis and follow-up time. In addition, it was revealed that there may be an association between renal involvement, GI involvement, or high CRP value at the time of diagnosis and steroid-dependent disease (Table 4). In Model 1, where only male patients were considered to evaluate the effect of scrotal involvement, it was shown that the presence of scrotal involvement may also be related to steroid-dependent disease (Table 4). Similar to our study, Liao et al.[15] showed that the increase in age of onset and the presence of renal involvement were associated with steroid-dependent disease, but they did not investigate its relationship with GI involvement.

Recurrence of IgAV in children can be seen at a rate of 2.7 to 66.2%.[2,17,37-40] The wide range in these rates is mainly based on the different definition criteria of recurrence among studies. In our study, we defined recurrence as the recurrence of clinical findings of IgAV at least three months after discontinuation of all drugs, consistent with previous epidemiological studies,[17,18,37] and we showed that recurrence developed in 6.9% of patients. Risk factors for renal recurrence in IgAV were determined as patients being over 10 years

of age, severe intestinal angina, and persistent purpura.[30] In a population-based study, renal involvement, allergic rhinitis, and steroid use for more than 10 days were shown as risk factors for IgAV recurrence in children.[19] In a study investigating the relationship between recurrence and laboratory indices, a relationship was found between disease duration, joint involvement, and recurrence.[41] In our data, we showed that GI involvement was the only associated factor for recurrence.

In childhood, IgAV usually has a self-limiting course and less refractory disease occurs than in adults.[9,12,13] Age at disease onset and the presence of renal involvement have been shown to be risk factors for refractory disease in previous studies.[15] In IgAV patients with GI involvement, EBV and CMV infections have been shown to play a role in refractory disease.[42] In our IgAV cohort, all refractory patients had renal involvement. In multivariable analyses, we established that the increase in the age of disease onset and follow-up duration was an associated factor for refractory disease. We think that children with renal involvement and those diagnosed with IgAV at a relatively older age should be followed more closely in terms of refractory disease.

Our study has limitations, such as its single-center and retrospective design. In addition, our clinic is a tertiary health center, and more severe cases are referred to us, which may cause bias in patient selection; therefore, our results cannot reflect the entire patient population. However, this is one of the few studies investigating the effect of age at disease onset on clinical findings in IgAV cases in detail, and the study includes a large cohort of patients, making our study powerful.

In conclusion, the age of onset of the disease has an effect on clinical features and disease outcomes in pediatric IgAV patients. Age at diagnosis and follow-up time may be associated with renal involvement and refractory and steroid-dependent disease in IgAV. In addition, there may be a relationship between steroid-dependent disease and renal, GI, and scrotal involvement, as well as between GI involvement and recurrence. We believe that these real-life data will be useful to clinicians in IgAV follow-up.

Ethics Committee Approval: The study protocol was approved by the Gazi University Faculty of Medicine Ethics Committee (date: 07.08.2020, no: 506). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: Since the current study is a retrospective design, consent from the participants was not required.

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

Author Contributions: All authors contributed equally to the article.

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REFERENCES

1. Saulsbury FT. Clinical update: Henoch-Schönlein purpura. Lancet 2007;369:976-8. doi: 10.1016/S0140-6736(07)60474-7.
2. Trapani S, Micheli A, Grisolia F, Resti M, Chiappini E, Falcini F, et al. Henoch Schonlein purpura in childhood: Epidemiological and clinical analysis of 150 cases over a 5-year period and review of literature. Semin Arthritis Rheum 2005;35:143-53. doi: 10.1016/j.semarthrit.2005.08.007.
3. Gardner-Medwin JM, Dolezalova P, Cummins C, Southwood TR. Incidence of Henoch-Schönlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. Lancet 2002;360:1197-202. doi: 10.1016/S0140-6736(02)11279-7.
4. Calviño MC, Llorca J, García-Porrúa C, Fernández-Iglesias JL, Rodriguez-Ledo P, González-Gay MA. Henoch-Schönlein purpura in children from northwestern Spain: A 20-year epidemiologic and clinical study. Medicine (Baltimore) 2001;80:279-90. doi: 10.1097/00005792-200109000-00001.
5. Watson L, Richardson AR, Holt RC, Jones CA, Beresford MW. Henoch schonlein purpura--a 5-year review and proposed pathway. PLoS One 2012;7:e29512. doi: 10.1371/journal.pone.0029512.
6. Aalberse J, Dolman K, Ramnath G, Pereira RR, Davin JC. Henoch Schonlein purpura in children: An epidemiological study among Dutch paediatricians on incidence and diagnostic criteria. Ann Rheum Dis 2007;66:1648-50. doi: 10.1136/ard.2006.069187.
7. Weiss PF, Klink AJ, Localio R, Hall M, Hexem K, Burnham JM, et al. Corticosteroids may improve clinical outcomes during hospitalization for Henoch-Schönlein purpura. Pediatrics 2010;126:674-81. doi: 10.1542/peds.2009-3348.

8. Blanco R, Martínez-Taboada VM, Rodríguez-Valverde V, García-Fuentes M, González-Gay MA. Henoch-Schönlein purpura in adulthood and childhood: Two different expressions of the same syndrome. Arthritis Rheum 1997;40:859-64. doi: 10.1002/art.1780400513.
9. Kang Y, Park JS, Ha YJ, Kang MI, Park HJ, Lee SW, et al. Differences in clinical manifestations and outcomes between adult and child patients with Henoch-Schönlein purpura. J Korean Med Sci 2014;29:198-203. doi: 10.3346/jkms.2014.29.2.198.
10. Hung SP, Yang YH, Lin YT, Wang LC, Lee JH, Chiang BL. Clinical manifestations and outcomes of Henoch-Schönlein purpura: Comparison between adults and children. Pediatr Neonatol 2009;50:162-8. doi: 10.1016/S1875-9572(09)60056-5.
11. Uppal SS, Hussain MA, Al-Raqum HA, Nampoory MR, Al-Saeid K, Al-Assousi A, et al. Henoch-Schönlein's purpura in adults versus children/adolescents: A comparative study. Clin Exp Rheumatol 2006;24(2 Suppl 41):S26-30.
12. García-Porrúa C, Calviño MC, Llorca J, Couselo JM, González-Gay MA. Henoch-Schönlein purpura in children and adults: Clinical differences in a defined population. Semin Arthritis Rheum 2002;32:149-56. doi: 10.1053/sarh.2002.33980.
13. Pillebout E, Thervet E, Hill G, Alberti C, Vanhille P, Nochy D. Henoch-Schönlein purpura in adults: Outcome and prognostic factors. J Am Soc Nephrol 2002;13:1271-8. doi: 10.1097/01.asn.0000013883.99976.22.
14. Ghrahani R, Ledika MA, Sapartini G, Setiabudiawan B. Age of onset as a risk factor of renal involvement in Henoch-Schönlein purpura. Asia Pac Allergy 2014;4:42-7. doi: 10.5415/apallergy.2014.4.1.42.
15. Liao CH, Tsai M, Yang YH, Chiang BL, Wang LC. Onset age is a risk factor for refractory pediatric IgA vasculitis: A retrospective cohort study. Pediatr Rheumatol Online J 2020;18:86. doi: 10.1186/s12969-020-00480-3.
16. Ozen S, Pistorio A, Iusan SM, Bakkaloglu A, Herlin T, Brik R, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. Ann Rheum Dis 2010;69:798-806. doi: 10.1136/ard.2009.116657.
17. Alfredo CS, Nunes NA, Len CA, Barbosa CM, Terreri MT, Hilário MO. Henoch-Schönlein purpura: Recurrence and chronicity. J Pediatr (Rio J) 2007;83:177-80. doi: 10.2223/JPED.1595.
18. Teng MC, Wang LC, Yu HH, Lee JH, Yang YH, Chiang BL. Kawasaki disease and Henoch-Schönlein purpura - 10 years' experience of childhood vasculitis at a university hospital in Taiwan. J Microbiol Immunol Infect 2012;45:22-30. doi: 10.1016/j.jmii.2011.09.024.
19. Lei WT, Tsai PL, Chu SH, Kao YH, Lin CY, Fang LC, et al. Incidence and risk factors for recurrent Henoch-Schönlein purpura in children from a 16-year nationwide database. Pediatr Rheumatol Online J 2018;16:25. doi: 10.1186/s12969-018-0247-8.
20. Gupta V, Aggarwal A, Gupta R, Chandra Chowdhury A, Agarwal V, Lawrence A, et al. Differences between adult and pediatric onset Henoch-Schonlein purpura from North India. Int J Rheum Dis 2018;21:292-8. doi: 10.1111/1756-185X.13221.
21. Batu ED, Sarı A, Erden A, Sönmez HE, Armağan B, Kalyoncu U, et al. Comparing immunoglobulin A vasculitis (Henoch-Schönlein purpura) in children and adults: A single-centre study from Turkey. Scand J Rheumatol 2018;47:481-6. doi: 10.1080/03009742.2018.1448111.
22. Peruzzi L, Coppo R. IgA vasculitis nephritis in children and adults: One or different entities? Pediatr Nephrol 2021;36:2615-25. doi: 10.1007/s00467-020-04818-7.
23. Lin SJ, Huang JL. Henoch-Schönlein purpura in Chinese children and adults. Asian Pac J Allergy Immunol 1998;16:21-5.
24. Lu S, Liu D, Xiao J, Yuan W, Wang X, Zhang X, et al. Comparison between adults and children with Henoch-Schönlein purpura nephritis. Pediatr Nephrol 2015;30:791-6. doi: 10.1007/s00467-014-3016-z.
25. Penido MGMG, Palma LMP. IgA vasculitis in children. J Bras Nefrol 2022;44:3-5. doi: 10.1590/2175-8239-JBN-2022-E002.
26. Peru H, Soylemezoglu O, Bakkaloglu SA, Elmas S, Bozkaya D, Elmaci AM, et al. Henoch Schonlein purpura in childhood: Clinical analysis of 254 cases over a 3-year period. Clin Rheumatol 2008 ;27:1087-92. doi: 10.1007/s10067-008-0868-2.
27. Leung AK, Chan KW. Evaluating the child with purpura. Am Fam Physician 2001;64:419-28.
28. Barut K, Şahin S, Adroviç A, Kasapçopur Ö. Diagnostic approach and current treatment options in childhood vasculitis. Turk Pediatri Ars 2015;50:194-205. doi: 10.5152/TurkPediatriArs.2015.2363.
29. Chan H, Tang YL, Lv XH, Zhang GF, Wang M, Yang HP, et al. Risk factors associated with renal involvement in childhood Henoch-Schönlein purpura: A meta-analysis. PLoS One 2016;11:e0167346. doi: 10.1371/journal.pone.0167346.
30. Shin JI, Park JM, Shin YH, Hwang DH, Kim JH, Lee JS. Predictive factors for nephritis, relapse, and significant proteinuria in childhood Henoch-Schönlein purpura. Scand J Rheumatol 2006;35:56-60. doi: 10.1080/03009740510026841.
31. Balslev T. Schoenlein-Henoch syndrome with acute scrotal condition simulating torsion of the testis. Ugeskr Laeger 1990;152:678.
32. Chamberlain RS, Greenberg LW. Scrotal involvement in Henoch-Schönlein purpura: A case report and review of the literature. Pediatr Emerg Care 1992;8:213-5. doi: 10.1097/00006565-199208000-00010.

33. Ha TS, Lee JS. Scrotal involvement in childhood Henoch-Schönlein purpura. Acta Paediatr 2007;96:552-5. doi: 10.1111/j.1651-2227.2006.00173.x.
34. Sunar Yayla EN, Bakkaloğlu SA. Clinical features of pediatric IgA vasculitis patients with scrotal involvement. Mod Rheumatol 2022:roac111. doi: 10.1093/mr/roac111.
35. Selewski DT, Ambruzs JM, Appel GB, Bomback AS, Matar RB, Cai Y, et al. Clinical characteristics and treatment patterns of children and adults with IgA nephropathy or IgA vasculitis: Findings from the CureGN study. Kidney Int Rep 2018;3:1373-84. doi: 10.1016/j.ekir.2018.07.021.
36. Rice JB, White AG, Scarpati LM, Wan G, Nelson WW. Long-term systemic corticosteroid exposure: A systematic literature review. Clin Ther 2017;39:2216-29. doi: 10.1016/j.clinthera.2017.09.011.
37. Prais D, Amir J, Nussinovitch M. Recurrent Henoch-Schönlein purpura in children. J Clin Rheumatol 2007;13:25-8. doi: 10.1097/01.rhu.0000255692.46165.19.
38. Calvo-Río V, Hernández JL, Ortiz-Sanjuán F, Loricera J, Palmou-Fontana N, González-Vela MC, et al. Relapses in patients with Henoch-Schönlein purpura: Analysis of 417 patients from a single center. Medicine (Baltimore) 2016;95:e4217. doi: 10.1097/MD.0000000000004217.
39. Fretzayas A, Sionti I, Moustaki M, Papadimitriou A, Nicolaidou P. Henoch-Schönlein purpura: A long-term prospective study in Greek children. J Clin Rheumatol 2008;14:324-31. doi: 10.1097/RHU.0b013e31817a240a.
40. Anil M, Aksu N, Kara OD, Bal A, Anil AB, Yavaşcan O, et al. Henoch-Schönlein purpura in children from western Turkey: A retrospective analysis of 430 cases. Turk J Pediatr 2009;51:429-36.
41. Zhou J, Li L, Luo J, Yang Y, Shen X. Association between common laboratory indices and IgAV recurrence in children. BMC Pediatr 2022;22:606. doi: 10.1186/s12887-022-03657-9.
42. Wang H, Zhang B, Li S, Ou R, Liu Y, Tan W. Clinical outcome in pediatric refractory gastrointestinal Henoch-Schönlein purpura treated with mycophenolate mofetil. Eur J Pediatr 2020;179:1361-6. doi: 10.1007/s00431-020-03592-w.