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ORIGINAL ARTICLE

The clinical spectrum of Henoch–Schönlein purpura in children: a single-center study

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Abstract

Objectives Henoch–Schönlein purpura (HSP) is the most common vasculitis of children. The aim of this study is to evaluate the demographic and clinic findings of patients with HSP and also to determine predictive factors for assessing the development of gastrointestinal system (GIS) and renal involvement.

Methods This study was performed prospectively among children with HSP who are under 18 years of age and being followed-up in the Pediatric Rheumatology Unit of Health Sciences University Kanuni Sultan Süleyman Training and Research Hospital between January 2016 and January 2018.

Results A total of 265 patients, 137 boys (51.7%) and 128 girls (48.3%), were involved to the study. The mean ± standard deviation of age at the diagnosis was 7.5 ± 3.2. The most common disease onset season was spring (31.7%). The rate of arthritis, GIS involvement, and renal involvement were 54%, 51.3%, and 29.1%, respectively. GIS bleeding was more frequent in males than females ($p = 0.007$). Boys over 7 years of age had significantly more common GIS bleeding ($p = 0.04$). Intussusception, relapse, and serious GIS involvement requiring hospitalization and steroid treatment were highly associated with severe renal involvement.

Conclusions We demonstrated that patients suffering intussusception, relapse, and serious GIS involvement or requiring hospitalization and steroid treatment had tendency to present with severe renal involvement. Therefore, these patients should be followed up carefully for not overlooking renal involvement of HSP.

Keywords Children · Gastrointestinal system involvement · Henoch–Schönlein purpura · Intussusception · Relapse · Renal involvement

Introduction

Henoch–Schönlein purpura (HSP), is the most common vasculitis of children with an annual incidence of 13–20/100,000 [1, 2]. According to a nationwide study, HSP was the most common vasculitis with the frequency of 81.6% in our country [3]. It typically involves small vessels of the skin, gastrointestinal tract, joints, and kidneys and usually manifests with cutaneous purpura, arthralgia, arthritis, abdominal pain, gastrointestinal hemorrhage, and glomerulonephritis [4]. Although it is considered to be self-limiting, gastrointestinal system (GIS), central nervous system, and/or renal involvement may give rise to morbidity and mortality in HSP. GIS involvement occurs in 50 to 75% of children, usually within a week after onset of the rash. The frequency of renal involvement varies from 20 to 60% of children [5] within 4 weeks of the diagnosis in 85% of cases, within 6 weeks in 91%, and within 6 months in 97% [6]. Thus, the researchers have focused on investigating the predictors for GIS and renal involvement. Predicting the risk factors at the time of diagnosis may facilitate the management of the disease. Some clinical and laboratory predictive factors of system involvements, such as onset at older age, persistent purpuric lesions, severe abdominal symptoms, the presence of relapse, low factor XIII activity, and neutrophil-to-lymphocyte ratio, have been

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previously described. However, there is still no standard and validated way of identifying the risk factors for system involvements. Therefore, we prospectively evaluated the children with HSP to better define the demographic findings and risk factors for GIS and/or renal involvement.

Material and methods

This study was performed among children with HSP who are under 18 years of age and being followed up in the Pediatric Rheumatology Unit of Health Sciences University Kanuni Sultan Süleyman Training and Research Hospital between January 2016 and January 2018. Patients were classified as having HSP according to the European League Against Rheumatism, Paediatric Rheumatology International Trials Organization and Paediatric Rheumatology European Society (EULAR/PRINTO/PRES) [4]. The population of our study consisted of all children referred to our pediatric rheumatology unit from pediatricians, pediatric nephrologists and pediatric emergency departments of either from our hospital or other primary and secondary centers. All children were examined by the same two pediatric rheumatology fellows and additionally evaluated by the experienced pediatric rheumatologist. The demographic data including age, gender, season of occurrence, presence of consanguinity, and clinical features related to HSP were recorded at the first visit by face-to-face interviews. Furthermore, all patients were questioned for predisposing factors including infections, vaccine, etc. at the first visit. Baseline and follow-up physical examination findings were also added to the patient's recordings at regular visits. Urinalysis was performed weekly at the first month of the disease, biweekly up to 3 months, monthly until 6 months, and up to 2 years in 3-month periods. Newly emerging symptoms and signs if present were noted to their medical charts at each visit. The medications were also recorded in good order. Additional conditions such as history of hospitalization, length of stay at the hospital, pathology of biopsies, and time that patient relapsed after diagnosis of HSP were also recorded.

Abdominal involvement was defined as the presence of any of the following findings: (1) abdominal pain, (2) vomiting, (3) hematemesis, (4) melena, (5) massive GIS hemorrhage, and (6) intussusception. Patients were accepted as having severe GIS involvement in presence of GIS bleeding and/or intussusception. Renal involvement was defined according to the presence of any of the following findings: (1) hematuria (> 5 red blood cells/high power field), (2) red blood cell casts in urinary sediment, (3) proteinuria > 4 mg/m^2/h urine protein, (4) hypertension (systolic and/or diastolic blood pressures ≥ 95th percentile for gender, age, and height on ≥ 3 occasions), (5) nephrotic proteinuria (> 40 mg/m^2/h), and (6) renal insufficiency. Relapse was described as presence of a new disease-related symptom after an asymptomatic period of at least 3 months [7].

Renal biopsy was performed in the patients with nephrotic syndrome, nephrotic-range proteinuria, or persistent non-nephrotic proteinuria. Pathology of biopsy samples were evaluated according to the Oxford classification [8, 9].

Mediterranean fever (*MEFV*) mutation analysis was performed in patients with a severe disease course or relapse by Sanger sequencing. Patients were diagnosed with familial Mediterranean fever (FMF) based on pediatric FMF criteria [10]. According to aforementioned criteria, patients can be classified as having FMF in presence of at least two following findings: (1) fever; axillary temperature of > 38 °C, 6–72 h of duration, ≥ 3 attacks; (2) abdominal pain, 6–72 h of duration, ≥ 3 attacks; (3) chest pain, 6–72 h of duration, ≥ 3 attacks; (4) arthritis, 6–72 h of duration, ≥ 3 attacks; (5) family history of FMF [10].

All patients were anonymous. The parents and patients gave a general consent approving anonymous data use for academic purpose. The study protocol was approved by the local Ethical Committee.

Statistical analysis

SPSS software version 22 was used to evaluate the statistical analysis. Continuous data were described as mean, standard deviation (SD) medians, minimum (min), and maximum (max) values and categorical variables as percentages. The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov–Smirnov/Shapiro–Wilk's test) to determine whether or not they are normally distributed. Categorical variables were compared with the chi-square test or Fisher's exact test where appropriate. Student *t* test or Mann–Whitney *U* test was used to compare the continuous data between the two groups where appropriate. A *p* value of less than 0.05 was considered to show a statistically significant result.

Results

A total of 265 patients were involved to the study. The mean ± SD of age at the diagnosis was 7.5 ± 3.2. Males were consisting 51.7% ($n = 137$) of the patients. The mean ± SD follow-up time was 1.3 ± 0.7 (0.5–2.5) years.

The most common disease onset season was spring (31.7%), followed by winter (30.2%), autumn (23.4%), and summer (14.7%). Among them, 98 patients (36.9%) reported a predisposing factor. Of those, 67 patients had a history of upper respiratory infection and 31 had gastrointestinal tract infections. In laboratory work-up, there was not any evidence of infections.

All the patients had palpable purpura. Among 265 patients, 153 (57.7%) had arthritis, 136 (51.3%) had GIS involvement, of whom 28 (20.5%) had GIS bleeding and 6 (4.4%) had intussusception. Renal involvement was present in 77 (29.1%) children. Of them, 54 had non-nephrotic-range proteinuria and 6 had nephrotic-range proteinuria. The main clinical and laboratory findings are summarized in Table 1. There were not any seasonal differences in terms of distribution of clinical findings except hematochezia. The largest group of patients with hematochezia was admitted to hospital in summer [$n = 6$ (35.3%), $p = 0.003$].

One hundred three patients (38.9%) were hospitalized, and the mean ± SD hospitalization time was 9 ± 6.5 days. Furthermore, two patients with massive GIS bleeding were admitted to the pediatric intensive care unit (PICU). Two patients underwent to surgery for intussusception. Renal insufficiency, central nervous system, or pulmonary system involvement was not observed in any of our patients. Mortality was not detected during follow-up. Twelve (4.6%) patients had a relapse. The median (min–max) time of relapse was 1.5 (0.5–2) years.

During the course of disease, 92 (34.7%) patients received methylprednisolone (2 mg/kg/day) at the beginning and tapered slowly according to patient's clinic. Nineteen (7.2%) were treated with pulse methylprednisolone (30 mg/kg) due to severe GIS or renal involvement. Non-steroidal anti-inflammatory drugs (NSAIDs) were administered to 143 (54%) patients. Nine (3.4%) patients had received cyclophosphamide for renal involvement, and three (1.1%) were treated with mycophenolate mofetil because of GIS bleeding. Colchicine was given to eight patients. Furthermore, two patients who were hospitalized in PICU due to severe GIS bleeding were treated with plasmapheresis.

Renal biopsy was performed to 13 patients. Biopsy samples revealed minimal glomerular abnormalities without crescents (stage 1) in 3, mesangial proliferation without crescents (stage 2) in 4, mesangial proliferation with crescents in < 50% of glomeruli (stage 3) in 5, and mesangial proliferation with crescents in > 75% of glomeruli (stage 5) in 1 patient.

Presence of GIS involvement was neither related to the gender of the patient nor the clinical features like fever, subcutaneous edema, scrotal, and renal involvement. But, even though not reaching to statistical significance, arthritis was slightly more common in patients with GIS involvement. Nephrotic proteinuria and performance of biopsy procedure were significantly more common among the patients that were hospitalized due to severe GIS involvement and received steroids ($p = 0.01$).

Intussusception was statistically more common in patients with renal involvement ($p = 0.002$). Nephrotic proteinuria and performance of biopsy procedure were more common among relapsing patients ($p = 0.004$). Fever, subcutaneous edema, and scrotal involvement were statistically more frequent in patients presenting with arthritis compared to others ($n = 45$ vs $n = 26$, $p = 0.04$, $n = 92$ vs $n = 44$, $p < 0.01$, $n = 6$ vs $n = 0$, $p = 0.02$, respectively).

MEFV mutation analysis was performed in 32 (12%) patients. Fourteen (43.8%) of them carried mutations at least one allele (Table 2). When their medical history was evaluated retrospectively, other features supporting the clinic of FMF disease were identified in eight patients. All of these patients were classified as having FMF according to pediatric FMF criteria. Thus, colchicine treatment was started.

When patients were compared according to gender, GIS bleeding was more frequent in males than females ($n = 24$ vs $n = 4$, $p = 0.007$). In terms of other clinical findings, boys and girls were similar (Fig. 1). Boys younger than 7 years had significantly more common GIS involvement (61.1% vs 43.5, $p = 0.04$), but when boys are 7 or older, they had significantly more common GIS bleeding (10.1% vs 23.1%, $p = 0.04$).

Table 1 The main clinical and laboratory findings of the patients

Fever, *n* (%)	71 (26.8)
Arthralgia, *n* (%)	157 (59.2)
Arthritis, *n* (%)	153 (57.7)
Subcutaneous edema, *n* (%)	136 (51.3)
Gastrointestinal involvement, *n* (%)	136 (51.3)
Abdominal pain	136 (51.3)
Hematochezia	17 (6.4)
Melena	11 (4.2)
Intussusception	6 (2.3)
Pancreatitis and cholecystitis	1 (0.4)
Renal involvement, *n* (%)	77 (29.1)
Hematuria	45 (17)
Non-nephrotic proteinuria	54 (20.4)
Nephrotic proteinuria	6 (2.3)
Renal insufficiency	0 (0)
Biopsy proven nephritis	13 (4.9)
Scrotal involvement, *n* (%)	6 (2.3)

Table 2 The Mediterranean fever variants in the patients

M694V/M680I, *n* (%)	2 (14.3)
M694V/E148Q, *n* (%)	2 (14.3)
V726A/K695R, *n* (%)	1 (7.1)
E148Q/E148Q, *n* (%)	1 (7.1)
M694V/-, *n* (%)	5 (35.8)
E148Q/-, *n* (%)	2 (14.3)
V726A/-, *n* (%)	1 (7.1)

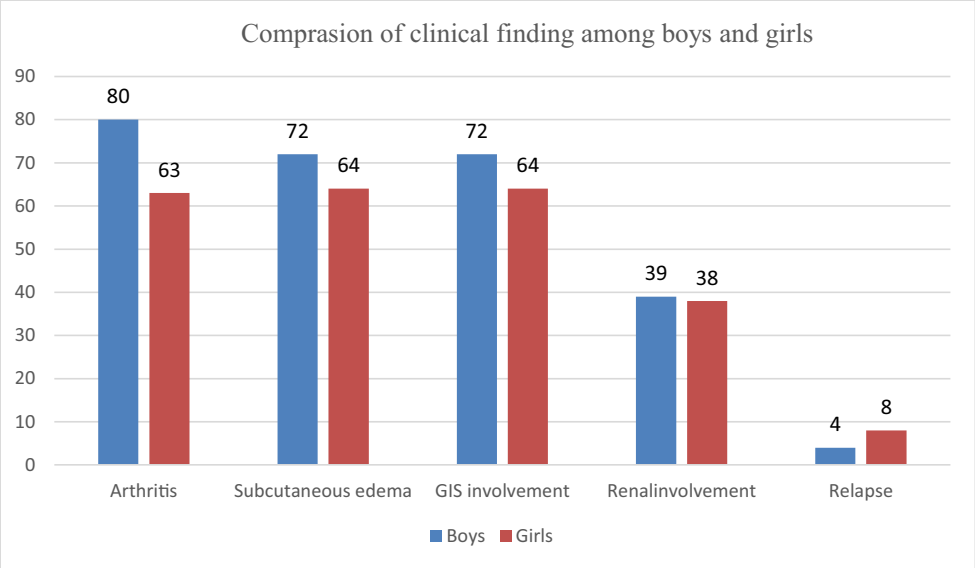

Fig. 1 Comparison of clinical finding among boys and girls. $p > 0.05$

Discussion

HSP is characterized by palpable purpura predominantly localized at the lower extremities, arthritis, subcutaneous edema, GIS, and renal involvement. To our knowledge, our study is the only patient series evaluating the demographic and clinical features of HSP from a single pediatric rheumatology center in Turkey. We have demonstrated that children with intussusception and severe GIS involvement that were in need of hospitalization and steroid therapy had significantly more serious renal involvement requiring renal biopsy due to nephrotic proteinuria. The relapse rate of HSP was found to be increased in patients with serious renal involvement.

The occurrence of HSP is most frequent between the ages of 3 and 15 years [11]. The disease makes a peak between ages of 5–7 years [1, 2, 12]. But, reports from our country claim that the mean age of HSP is ranging between 7 and 10 years [3, 13–16]. We found similar mean age of onset of HSP that was 7.5 ± 3.2 years. According to our study, males (51.7%) and females (48.3%) were affected nearly equally. However, there are studies showing either male [15, 17–22] or female dominance [22, 23].

The development of HSP varies seasonally. Although winter and autumn were the most frequent seasons of the disease occurrence [2, 20, 21, 24–26], some studies report spring as the peak season. The biggest nationwide study from Korea also reported that the disease was predominantly occurring in the spring [27]. One of the largest series presented by Hwang et al. demonstrated spring as the main season of HSP emergence too [22]. Similar to these large series, we have found that most of our cases had presented in the spring, while summer was the season that disease had ensued least. Geographical variations may be one of the factors bringing the difference of mean age of occurrence and seasonality of HSP in the literature. The etiopathogenesis of HSP is not displayed fully yet. It is believed to occur after upper respiratory tract infections and other common infectious diseases of childhood [28]. Seasonal differences in the emergence of the HSP may also support the infectious agents as the main causatives of the disease. Vaccines, drugs, and nutrients may also be the triggering factors [11].

A Korean study about seasonality reported that, unlike the other age groups, patients in the adolescent group was more commonly affected in summer than during in autumn [22]. They proposed that enteroviruses that occur in summer may be the reason of the difference according to age. In our study, although no age predominance was determined, we demonstrated that patients had higher rates of GIS bleeding when the disease occurred in summer. Similar to Korean authors, we put forward that agents like enteroviruses out-breaking especially in summer may be the cause of more frequent GIS bleeding occurring in these months. A clear cause for this increase in incidence could not be shown, and additional seasonality studies are needed to determine the disease association with viruses. In presented study, 67 patients had a history of upper respiratory infection and 31 had gastrointestinal tract infections. However, we did not demonstrate any evidence of infection among these patients.

Hospitalization rate of our study group was 38.9%. Likely, one of the largest nationwide surveys from Taiwan reported their hospitalization rate as 40.5% [2] However, the largest Korean nationwide epidemiologic study reported a lower rate of hospitalization (11.3%) [27]. The severity of the disease and indications for hospitalization may be different between countries. HSP is an acute disease that may end with very rapid deterioration, especially when GIS involvement is the subject. So, social indications like family's anxiety and level of perception of disease and its outcome may be the case while

physicians are making their decision. In our cohort, GIS involvement was the most common reason for hospitalization (92.2%). Majority of them were treated with 2 mg/kg/day or 30 mg/kg methylprednisolone according to the severity of the disease. In addition, 3 patients were admitted because of severe infected bullous skin lesions and 5 for severe subcutaneous edema and arthritis limiting their mobilization.

Palpable purpura is the leading criteria of HSP diagnosis. All of our patients had palpable purpura, mostly present at the beginning of disease (*n* 231, 87.2%), while some had purpuric rash after joint or GIS symptoms (*n* 34, 12.8%). According to the literature, joint involvement is the second most common clinical finding [4]. Arthritis and arthralgia were reported in 50–80% of patients in HSP [11]. Besides, there are studies reporting higher rates of arthritis; Fretzayas et al. reported the rate of arthritis as 91.9% of their cohort [24]. In our study, arthritis and arthralgia frequencies were 54% and 59%, respectively.

Gastrointestinal system involvement has been shown to occur in 40 to 80% of children with HSP [3, 4, 29, 30]. In our study, the incidence of GIS involvement was 51.3%. Of those, serious GIS involvement was defined as GIS bleeding (*n* 28, 20.6%), intussusception (*n* 6, 4.4%), and pancreatitis (*n* 1, 0.7%). Ten patients with severe GIS bleeding were treated with pulse steroid. Due to severe uncontrollable GIS bleeding, two of them were admitted to the PICU and one had hypovolemic shock during follow-up in PICU. Both were successfully treated with mycophenolate mofetil concomitant to plasmapheresis, and their massive bleedings improved quickly. Although plasmapheresis is one of the treatment options at rapidly progressive HSP nephritis and nephritic-range proteinuria [31], it has been also suggested as a life-saving option for severe GIS bleeding in adults and children [32–34]. According to our two successfully treated HSP cases with severe GIS bleeding that were unresponsive to steroid and immunosuppressant therapy, we can say that plasmapheresis may be an effective option in very resistant cases. Further studies related to that alternative approach are needed. Mycophenolate mofetil treatment also seems to be a good treatment option in severe GIS bleeding.

Intussusception is the most common surgical complication developing in 0.7–13.6% of children with HSP [35]. Six (2.3%) of our patients had intussusception and all were under 7 years of age. Two of them were operated, and one had extensive bowel resection and she recovered without any complication. One patient underwent pneumatic reduction for intussusception. The other three patients got well with steroid treatment; neither surgery nor pneumatic reduction was required. Pancreatitis is a very rarely reported feature of HSP. Zhang et al. outlined 13 pancreatitis cases at their cohort concerning 3212 children with HSP (0.4%) [36]. Similarly, Chen et al. reported one HSP-related pancreatitis (0.48%) among 208 of their patients with HSP [30]. As in these studies, our frequency of pancreatitis was 0.4% and only one patient suffered a severe episode of pancreatitis.

Our study displayed that males had more frequent GIS bleeding than girls and boys under 7 years of age had milder GIS symptoms such as colicky abdominal pain, whereas after 7 years of age, they come up with more serious GIS symptoms as massive GIS bleeding. However, age was not depicted as a significant factor for estimating the severity of GIS involvement in girls. When clinical features were taken in to account, none of them was operative while predicting the severity of GIS involvement. Yet, not reaching to significance, arthritis was found to show up more commonly in patients with GIS involvement.

In the literature, renal involvement in HSP was reported as 20–60% [3, 21, 25, 26, 37, 38]. The reason for this large range may be the origin of published data. We know that these reports were from pediatric units, nephrology units, or rheumatology units. In these different clinics, patient selection might have bias, either mild or severe cases may be selected. For instance, number of HSP cases with renal involvement may be higher in reports from nephrology units [17] and milder cases may be reported more commonly from pediatrics units [39]. We argued that our study had no such selection bias, as all the patients that had the diagnosis of HSP regardless of their organ involvement were included to our cohort. We found that renal involvement was seen in 29.1% of the patients, mostly in the first 3 months of the disease. One patient had renal involvement after 9 months, and one had after 13 months of their diagnosis. It is usually recommended that patients with HSP should be followed up for a minimum of 6 months to detect renal involvement [11] . Though it is rare, renal involvement may occur later on, especially if there is evidence of isolated hematuria or proteinuria. Thirteen (4.9%) of our patients underwent renal biopsy because of nephrotic or persistent non-nephrotic proteinuria. In all patients undergoing biopsy, HSP nephritis from minimal glomerular changes to diffuse crescent formation had revealed. Pulse methyl prednisolone treatment was given to all 13 patients and additional cyclophosphamide therapy was applied to 9 of them. Angiotensin-converting enzyme inhibitors were used in 34 (12.8%) patients with persistent non-nephrotic proteinuria. None of our patients had renal insufficiency or end-stage renal disease.

Until now, there are numerous studies to determine a predictive factor for assessing development of nephritis in HSP. Age was considered as an important aspect for foreseeing

renal involvement [17, 37–40]. However, we did not find any relationship between age and renal involvement. GIS involvement at the onset of HSP has been suggested as another anticipating factor for nephritis [37, 38]. Our patients with intussusception had higher rates of serious renal involvement. Three of six patients who developed intussusception underwent renal biopsy due to nephritic-range proteinuria. They had abnormal urine tests at the beginning of the disease. Mild GIS features were not found to be related to renal involvement, but severe abdominal pain requiring hospitalization and steroid therapy was significant for predicting kidney disease. So, these patients should be closely monitored for renal involvement.

There are studies revealing association between relapse and presence of nephritis [7, 37, 38, 40, 41]. Only 12 (4.6%) of our patients had relapse, of whom one patient had relapse after 2 years, and one had relapse two times within a year following onset of HSP. Despite low number, relapses were found to be significantly higher in patients with nephritis. The frequency of relapses reported in previous studies was ranging from 2.7 to 66.2% [21, 26, 41, 42]. Prais et al. reported recurrence rate of their patients as 2.7% [43]. Similar to our study, a Chinese study revealed their relapse rate 4.81%, and they found renal involvement associated with relapse [40]. In studies with higher relapse rates, a relapse was defined as a new explosion of skin lesions or other clinical findings following resolution of disease for at least 2 weeks or 1 month [21, 26]. In our cohort, a relapse was defined as development of new clinical features of HSP 3 months after full recovery of initial HSP findings [7, 43]. As emphasized in these studies, we believe that the symptoms that appeared before 3 months were a prolonged course of HSP should not be considered as recurrence.

MEFV mutation analysis was performed in 32 (12%) suspected patients, because they had severe clinical course or relapse. At least one allele was detected in 14 (43.8%) of these patients. An increased rate of *MEFV* mutations had been shown among patients with HSP in the literature [44–47]. Yet, there is no consensus about the impact of *MEFV* gene mutations on the clinical severity of HSP. Our patients with MEFV mutations had subcutaneous edema and arthritis more frequently like in the cohort of Özçakar et al. [44].

The major limitation of this study is the short follow-up period of some children with HSP. But we are still following these patients, and it is planned to present long-term results of the study group in the future. Due to the prospective design of the study and heterogeneity of our patients from mild to severe disease course, we rely on our results in providing substantial information about clinical features of HSP and predictive factors of development of nephritis during follow-up.

In conclusion, patients requiring hospitalization and steroid therapy due to serious GIS involvement, and those having relapses were found to have an increased incidence of renal involvement. This analysis includes a high number of patients with HSP which will help to better define the demographic findings and risk factors for GIS and/or renal involvement in HSP, management and follow-up of the disease, and its related complications from the perspective of pediatric rheumatologists.

Compliance with ethical standards

The study protocol was approved by the local Ethical Committee. All patients were anonymous. The parents and patients gave a general consent approving anonymous data use for academic purpose. The study protocol was approved by the local Ethical Committee

Disclosures None.

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