Research Article

Primary vasculitis in children:
A clinical-epidemiological study

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Abstract

Introduction. Classification of primary vasculitis is difficult and little is known about prevalence in childhood.
Objective. To determine frequency, epidemiological data and clinical features of primary vasculitis in pediatric patients between May 2000 and May 2008.
Design. Observational, retrospective and descriptive study.
Materials and methods. We reviewed medical record data base of primary vasculitis in pediatric patients of between 0 and 16 years of age that met the established inclusion criteria.
Results. 47 patients, 29 boys and 18 girls were included. The average presentation age was 4 years (range: 7 months to 13 years). The most frequent vasculitis was Henoch Schönlein purpura with 33 cases (70 percent), followed by Kawasaki disease with 9 patients (19 percent), acute hemorrhagic edema of infancy with 3 cases (6 percent) and cutaneous panarteritis nodosa and Churg-Strauss syndrome with 1 case each (2 percent).
Conclusions. Primary vasculitis is rare in childhood. Henoch Schönlein purpura was most frequent in our patients. Kawasaki disease was the vasculitis with highest morbidity. Acute hemorrhagic edema of infancy was less frequent, showed less morbidity and appeared in children under two years of age. We also identified 2 cases of lower frequency vasculitis such as cutaneous panarteritis nodosa and Churg-Strauss syndrome (Dermatol Argent 2009; 15(6):411-419).

Key words: *vasculitis, vasculitides, childhood, children.*

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ABBREVIATIONS

ACR: American College of Rheumatology
AHEI: Acute hemorrhagic edema of infancy
ANCA: Antineutrophil cytoplasmic antibodies
ASTO: Antistreptolysin O antibodies
CPAN: Cutaneous panarteritis nodosa
CSS: Churg-Strauss syndrome
ESPN: European Society of Paediatric Nephrology
EULAR: European League against Rheumatism
HSP: Henoch-Schönlein purpura
ICD-9: Ninth review of the International Classification of Diseases
KD: Kawasaki disease
PAN: Panarteritis nodosa
PReS: Paediatric Rheumatology European Society
TA: Takayasu arteritis
TAA: Temporal artery arteritis
WG: Wegener's granulomatosis

Introduction

The term vasculitis refers to a broad group of clinically heterogeneous diseases with a common histological substrate, the presence of inflammatory infiltrate in the thickness of the blood vessel wall.[1]

In idiopathic or primary vasculitis, the triggering event has not been identified, and secondary vasculitis occurs in relation to specific factors such as infections, allergic reactions, adverse drug effects, and different neoplasias.[2] Primary or idiopathic forms comprise about 45-55 percent of the cases.[3-5] Several classifications have been suggested in order to unify diagnostic criteria, quite a difficult goal to achieve, especially because etiologies are unknown, there is overlapping in clinical manifestations of different entities, and defining patognomonic or specific signs are lacking.[6-10]

In 1993, a group of experts gathered in Chapel-Hill (North Carolina, U.S.A.) reached consensus about a classification intended to become an international unifying reference, where 10 types of vasculitis are defined.[11]

Many vasculitis affect both adults and children, for example Henoch-Schönlein purpura (HSP) and secondary vasculitis. But some vasculitis, such as Kawasaki disease (KD) and acute hemorrhagic edema of infancy (AHEI), involve children exclusively; others, such as temporal artery arteritis (TAA) do not affect children; and yet others, such as nodose panarteritis (PAN) or Wegener's granulomatosis (WG), have different etiological, clinical and prognosis features in pediatric patients.

In 2006, the European League against Rheumatism (EULAR) was convened through the vasculitis work group of the Paediatric Rheumatology European Society (PReS), with the collaboration of colleagues from the American College of Rheumatology (ACR) and the European Society of Paediatric Nephrology (ESPN), with the purpose of establishing vasculitis classification criteria in children: HSP, KD, PAN, WG, and Takayasu arteritis (TA).[12] This consensus did not assess criteria for Churg-Strauss syndrome (CSS) or AHEI.

Little is known about vasculitis incidence and prevalence at pediatric age, partly due the scanty amount of statistical records. According to data obtained from some reference centers, the condition may account for between 1 and 4 percent of pediatric rheumatology consultations.[13,14] Skin is a frequently involved organ, either from onset or during the evolution of the disease; however, as far as we know, no statistics on this disease exist in pediatric dermatology settings in Argentina.

The purpose of our work was to determine frequency, epidemiological features, and clinical findings of primary vasculitis observed in pediatric patients consulting our hospital between May 2000 and May 2008.

Material and methods

The design of our work is observational, descriptive and retrospective. It was performed by revision of clinical history medical records of patients with diagnosis of primary vasculitis, according to our hospital data base diagnosis codes (PECTRA 2000 system).

The study period comprised from May 1, 2000 to May 1, 2008. Inclusion criterion was diagnosis of primary vasculitis in pediatric patients (from birth to 16 years of age). To establish this diagnosis, we used the criteria from the EULAR/PReS12 consensus for HSP, KD and cutaneous panarteritis nodosa (CPAN), Chapel-Hill[11] diagnostic criteria for CSS, and clinical-epidemiological data appearing with a frequency equal or higher than 80 percent in a systematic revision of 294 patients with AHEI diagnosis[15] (**Table 1**).

The studied variables were the frequency of the different types of vasculitis and distribution by gender and age, generally and in particular, for each entity: cutaneous involvement, type and location of lesion, skin biopsy, history of previous infectious process, treatment and outcome. In addition, the following particulars were studied for each condition:

HSP: The presence and location of abdominal pain, arthritis or arthralgia, renal involvement defined by hematuria and/or proteinuria and/or alteration of renal function

KD: The presence of at least 5 days of persisting fever, cervical lymphadenopathy, coronary arterial involvement detected by echocardiography, involvement of another organ.

AHEI: General condition of the patient, involvement of another organ.

CPAN: Titration of antineutrophil cytoplasmic antibodies (ANCA); previous history of clinical streptococcal infection, or diagnosis by laboratory data (streptest and/or culture and/or increase of antistreptolysin O antibodies (ASTO) for a normal value <200 IU/ml); involvement of another organ, myalgia or muscular tenderness; arterial hypertension according to age and gender percentiles, as suggested by the Argentine Pediatric Society [*Sociedad Argentina de Pediatría*]; the presence of mono- or polyneuropathy, and testicular pain or tenderness.

CSS: Personal history of asthma, eosinophilia, mono- or polyneuropathy, fixed pulmonary infiltrates assessed with image studies (chest X-ray, computarized tomography).

Statistical analysis of 95 percent confidence interval (95% CI) was done by VCCSTAT 0.12 version beta 2002.

Results

Of the 62 cases referred as pediatric primary vasculitis found according to the ninth revision codes of the International Classification of Diseases (ICD-9), 47 patients met the inclusion criteria (**Table 2**).

Twenty nine cases (62 percent; 95 percent CI: 46-75 percent) were male and 18 (38 percent; 95 percent CI: 24-53 percent) were female. Average presentation age was 4 years, with a range of 7 months to 13 years.

Most frequent vasculitis was HSP with 33 records (70 percent; 95 percent CI: 55-82 percent). Following in frequency were KD with 9 cases (19 percent; 95 percent CI: 9-33 percent), AHEI with 3 cases (6 percent; 95 percent CI: 1-17 percent), and CPAN and CSS with 1 case (2 percent; 95 percent CI: 0.1-11 percent) each (**Chart 1**).

TABLE 1. DIAGNOSTIC CRITERIA.

Henoch-Schönlein purpura[12]
Palpable purpura in the presence of one of the following criteria:
• Diffuse abdominal pain
• Skin biopsy with predominant IgA deposit
• Arthritis or arthralgia (acute, any joint)
• Renal involvement (hematuria and/or proteinuria)
Kawasaki disease[12]
At least 5 days persistent fever, in addition to four of the following criteria:
• Changes in peripheral extremities or perineal area
• Polymorphic exanthema
• Bilateral conjunctival injection
• Lip and oral cavity changes
• Cervical lymphadenopathy
In the case of arterial coronary involvement (detected by echocardiography) and fever, less than 4 criteria suffice (the exact figure is being subject to review).
Cutaneous panarteritis nodosa[12]
• Painful nodules and purpuric lesions without systemic involvement
• Skin biopsy with non-granulomatous necrotizing vasculitis
• Negative antineutrophil antibodies (ANCA) test
• Association with Group A β-hemolytic *Streptococcus pyogenes*
Acute hemorrhagic edema of infancy[15]
• Age range 6 to 24 months
• Good general condition, without systemic involvement, resolution without sequelae
• Purpuric target-like lesions
• Edema of hands and feet
• Normal platelet count (= 150000/mm^3)
Churg-Strauss syndrome[11]
Four or more of the following criteria:
• Asthma
• Skin biopsy with eosinophile extravasation
• Peripheral neuropathy (mono- or polyneuropathy)
• Eosinophilia > 10%
• Sinusitis
• Non-fixed pulmonary infiltrate in chest X-ray

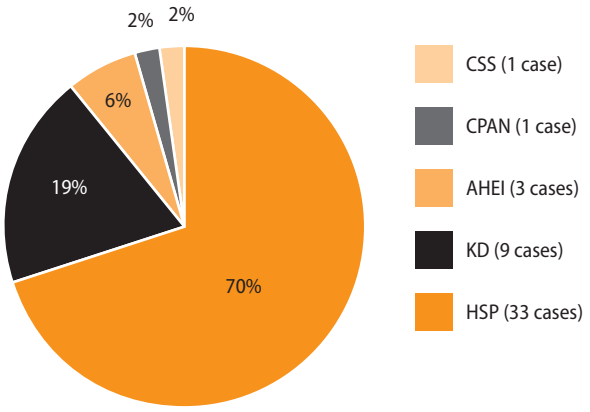


Chart 1. *Distribution by included vasculitis types.*

TABLE 2. STUDY POPULATION

Vasculitis	n	Average age (range)	Gender	
			Male	Female
HSP	33	5 years (2 - 12 years)	19	14
KD	9	23 months (4 months - 7 years)	5	4
AHEI	3	13 months (7 - 23 months)	2	1
CPAN	1	11 years	1	-
CSS	1	13 years	1	-
Total	**47**	**4 años (7 months - 13 years)**	**28**	**19**

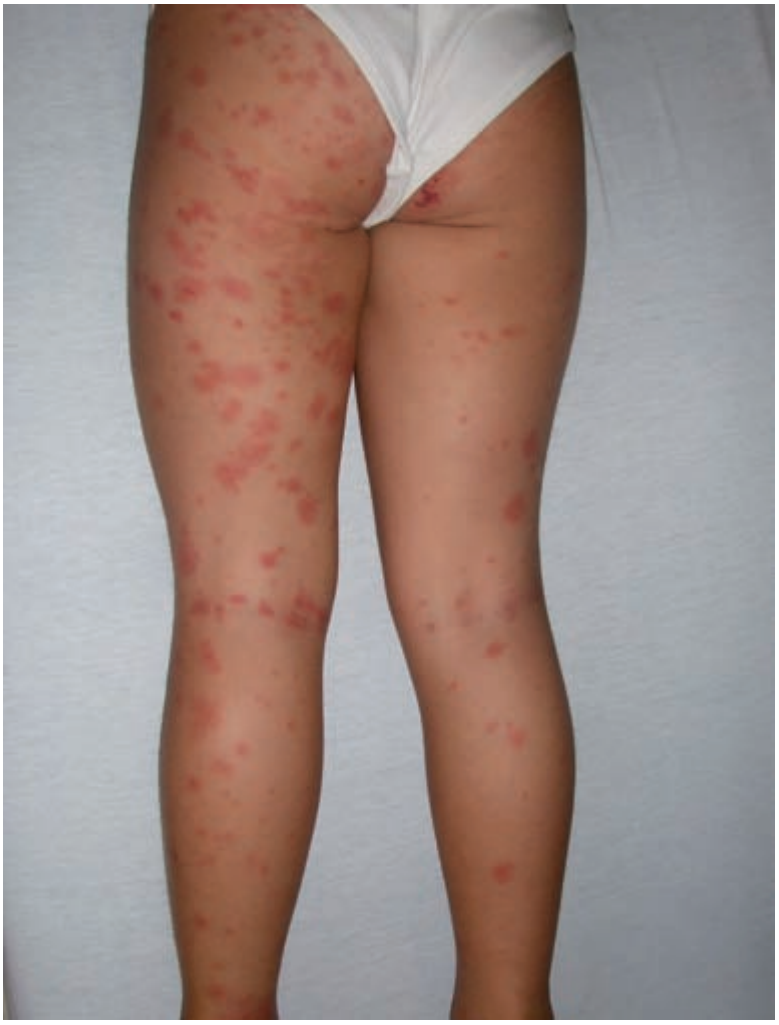
TABLE 3. HENOCH-SCHÖNLEIN PURPURA.

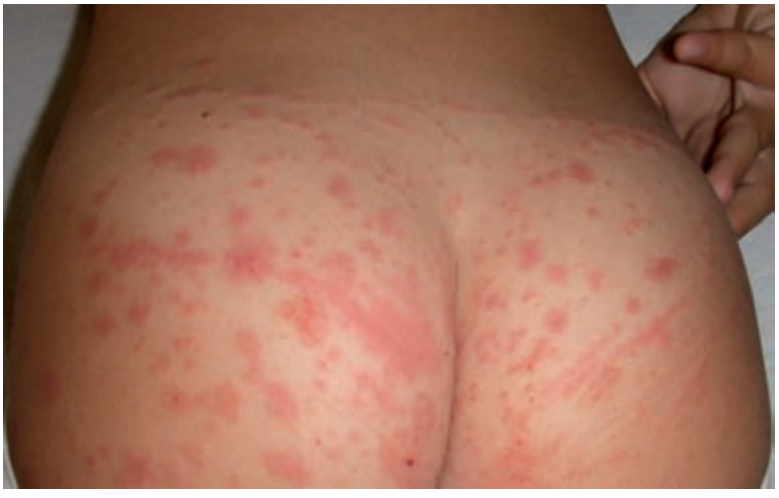
HSP	total n = 33	Percentage
Palpable purpura	33	100%
Arthritis or arthralgia	30	90%
Abdominal pain	19	57%
Renal involvement	8	24%
History of infection	18	55%
History of immunization	3	9%
Hospitalization	12	36%
Corticosterids	11	33%

Henoch-Schönlein purpura (Table 3)

Fourty seven cases of HSP were reported, whereof 33 fulfilled inclusion criteria. Nineteen patients (58 percent) were male and 14 (42 percent) were female. The average age at onset was 5 years, with a range of 2 to 12 years. All cases showed palpable purpura involving lower extremities with the classic distribution pattern on the buttocks and legs, and 8 cases also had purpura lesions in upper extremities, 4 in trunk, and 2 in the face (**Figures 1** and **2**). One patient showed bullous and necrotic lesions. Four patients had scalp edema, associated with pain in 2 cases. Two patients had scrotal swelling. Arthritis or arthralgia appeared in 90 percent (30/33): 22/30 in ankles, 10/30 in knees, 5/30 in hands and wrists, and less involvement in other joints such as feet, elbows and vertebral area. Abdominal involvement was present in 57 percent (19/33) of patients, and abdominal pain was the most frequent symptom. In 7 cases, abdominal ultrasonographies were indicated to address the cause of this pain; none of them showed evidence of occlusion or intestinal bleeding. Renal involvement appeared in 24 percent, one had macrogross hematuria, four had microhematuria, and three had proteinuria; none showed functional impairment. So far, no long-term involvement was detected in this organ. Of the 21 patients with arterial tension records, only 3 had hypertension according to the corresponding percentile;[16] all resolved the condition throughout the disease evolution. Skin biopsies were obtained from 6 patients, and in all cases the histopathological diagnosis was leukocytoclastic vasculitis. Only two were studied by direct immunofluorescence, with positive result for type A immunoglobulin deposit.

Eighteen patients (55 percent) had a history of a previous infection: fourteen had respiratory infection, whereof 3 were pharingitis with isolation of group A β-hemolytic





Figures 1 y 2. *Henoch-Schönlein purpura: palpable purpura in lower extremities with distribution pattern on the buttocks and legs.*

Streptococcus pyogenes in throat swab culture; and 3 patients had pneumonia, two of them with positive IgM for *Mycoplasma pneumoniae*. In addition, three patients referred history of recent immunization. In one patient, *Escherichia coli* was isolated from an urinary infection. Fifteen patients were studied by Streptest, with a positive result in 6 cases. Thirty six percent (12/33) of the patients required hospitalization; most frequent causes were the need of intravenous treatment, renal involvement follow-up, and abdominal and joint pain control. The rest were controlled as outpatients. Eleven patients received systemic meprednisone treatment, the remaining evolved favorably with rest and nonsteroidal antiinflammatory drugs.

Kawasaki disease (Table 4)

We identified 10 KD cases, whereof nine fulfilled inclusion criteria. The average age at onset was 23 months, with a range from 4 months to 7 years. In regard to gender, there were no significant differences (5 males and 4 females). In all cases, fever occurred for over five days, and infectious cause was ruled out. Six cases (66 percent) had changes in distal extremities, 3 with edema of hand and feet, one associated with erythema, 2 with palmoplantar scaling, and another with pain and erythema on the same location. Only one case had perineal area scaling. Exanthema was present in 7 patients (78 percent), which was morbilliform type in 4 children, maculopapulous in 2, and polymorph in 1 (**Figure 3**). One case showed erythema about the BCG immunization scar. Seven patients (78 percent) had clinical manifestations in lips and oral mucosa. The most frequent manifestations in lips were erythema and lip fissures, and vesicles and scaling were also found. Four cases showed enanthema, and two cases showed erosions of the oral mucosa. Bilateral conjunctival injection in characteristic pericorneal area was found in 8 cases (89 percent), and cervical lymphadenopathies were identified. All were assessed by color Doppler echocardiography, and images showed left coronary artery aneurysms in 6 (66 percent) children, 2 associated with myocardial involvement, and one with pericarditis also. Additionally, the latter showed subclavian and humeral dilations. With respect to laboratory results, at the time of diagnosis all patients had increased erythrosedimentation rate, 7 had leukocitosis, of which three had thrombocytosis.

All received 2 g/kg/dose intravenous gammaglobulin and 80-100 mg/kg/day acetylsalicilic acid. Six responded to the first dose, 2 patients needed a second dose, and one required a third dose. Of the 6 patients with aneurysms, 4 resolved totally after the gammaglobulin treatment and 2 showed improvement without complete resolution of the

arterial dilations by the date of this report. Of the reversible complications, one patient had arterial hypertension and another had ocular involvement, which resolved by gammaglobulin administration; of the irreversible complications, one patient showed necrosis of the vasculitis affected extremity that forced amputation, and intestinal subocclusion requiring partial colectomy (**Figure 4**).

Acute hemorrhagic edema of infancy

Three cases of AHEI fulfilled all inclusion criteria. At the time of diagnosis, the ages were 7, 11, and 23 months. Two were males and one was female. Two had history of an upper respiratory condition, and one was recently immunized. All presented good general condition, with purpuric target-like lesions, ecchymosis dominantly in face and extremities, and hand and feet edema (**Figure 5**). Two showed the typical pinna involvement (**Figure 6**). Only one had oral mucosa purpura. One case showed small cervical and inguinal lymphadenopathies. One patient presented fever at the time of diagnosis, and no child had systemic involvement. Leukocytosis occurred in all cases, and two had increased erythrosedimentation rate. All patients received acetaminophen treatment as needed, and evolved with lesion resolution without cutaneous or systemic sequelae.

Cutaneous panarteritis nodosa

One 11-year-old male patient appeared with diagnosis of CPAN, fulfilling diagnostic criteria for this disease. Clinically, he showed multiple erythematous and painful nodules located in upper extremities, and other erythemato-purpuric ones on left sole and right ankle, associated with wrist arthralgia, and ankle arthritis (**Figure 7**). No livedo reticularis or ulcerations were observed. Also no myalgia, systemic arterial hypertension, neuropathy or testicular tenderness appeared. Dosage of antineutrophil antibodies was negative. No pharingitis appeared and streptest and throat culture were negative; however, a high 1250 IU/ml ASTO titration was detected. Hepatitis B serology was negative. Skin biopsy confirmed the presence of vasculitis in small dermo-hypodermal vessel and small arteries. The indicated treatment consisted of rest, nonsteroidal antiinflammatory drugs, meprednisone 60 mg/day and prophylactic penicillin. The patient had favorable outcome, without recurrences so far.

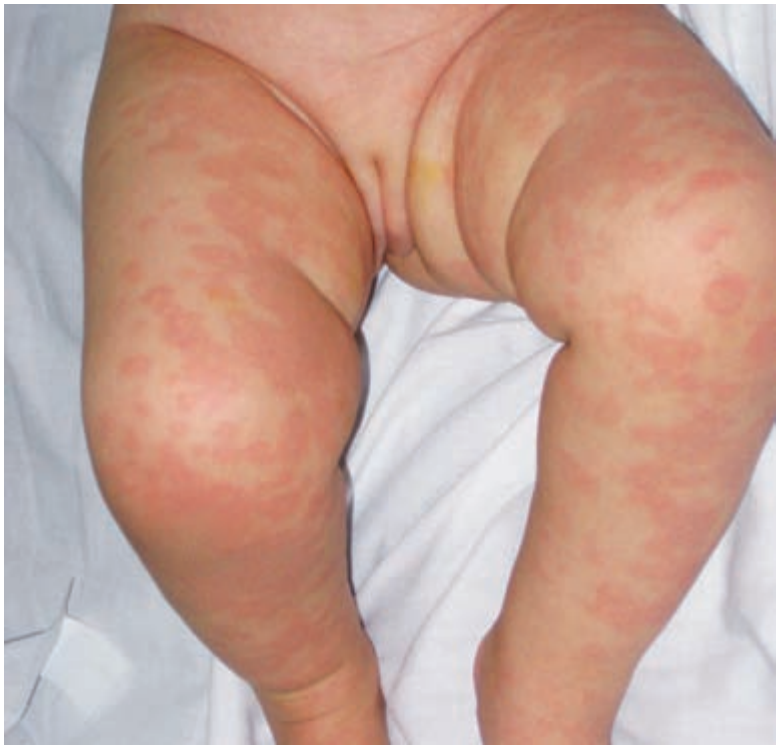


Figure 3. *Kawasaki disease: maculopapulous exanthema.*

TABLE 4. KAWASAKI DISEASE.

Case	Age	Fever	Exanthema	Cardiac involvement	Distal involvement	CI	Lips and mucosa	CA
1	36 m	+	Morbilliform	-	Pain, palmoplantarerythema	-	Lip erythema and fissure, perianal scaling	-
2	12 m	+	Erythematous and papulous	LC myocardial aneurysm	Palmoplantar scaling	+	Lip erythema	+
3	24 m	+	Morbilliform	-	Palmoplantar scaling	+	Lip scaling and fissure, oral erosions	+
4	84 m	+	-	LC aneurysm	-	+	No	+
5	12 m	+	Erythematous and papulous	LC and RC aneurisma	Edema and erythema of hands and feet	+	Lip erythema enanthema, erosions	+
6	4 m	+	Morbilliform	LC and RC aneurysm* Myocarditis Pericarditis Pericardial effusion	-	+	No	-
7	4 m	+	Erythematous	LC coronary aneurysm	Hand and feet edema	-	Lip erythema Enanthema	-
8	24 m	+	Polymorph	-	Hand and feet edema	+	Lip besicles and fissures, enanthema	+
9	10 m	+	Erythema	LC aneurysm	-	+	Enanthema	+

m: months. **F+:** fever of more than 5 days evolution. **CI:** conjunctival injection. **CA:** cervical lymphadenopathies. **LC:** left coronary. **RC:** right coronary.
***** Association with subclavian and humeral arteries.

Churg-Strauss syndrome

One 13-year-old male patient fulfilled diagnostic criteria of Churg-Strauss syndrome. Relevant history included recent diagnosis of Klinefelter syndrome and asthma of difficult control. He presented palpable purpuric lesions of lower extremities, myalgia, and sensitive and motor polyneuropathy (**Figure 8**).

Laboratory results included 24 percent eosinophilia (2160/mm^3), increased erythrosedimentation rate of 52 mm/h, 1/8192 IU/ml positive rheumatoid factor and 1/160 IU/ml positive ANCA-P. No alterations were found in the chest and paranasal sinus X-rays. Skin biopsy resulted in small and intermediate vessel leukocytoclastic vasculitis accompanied by eosinophilic infiltration. Direct immunofluorescence was negative. Kidney and peripheral nerve biopsies were also performed, thus confirming involvement. He was treated with three pulses of 500 mg/day/dose metilprednisolone and then 50 mg/day azathioprine for five days, with little response, and pulses of 750 mg/day cyclophosphamide were indicated, with favorable outcome. Currently, no active lesions appear on skin, renal function is normal and neurological signs have improved noticeably.

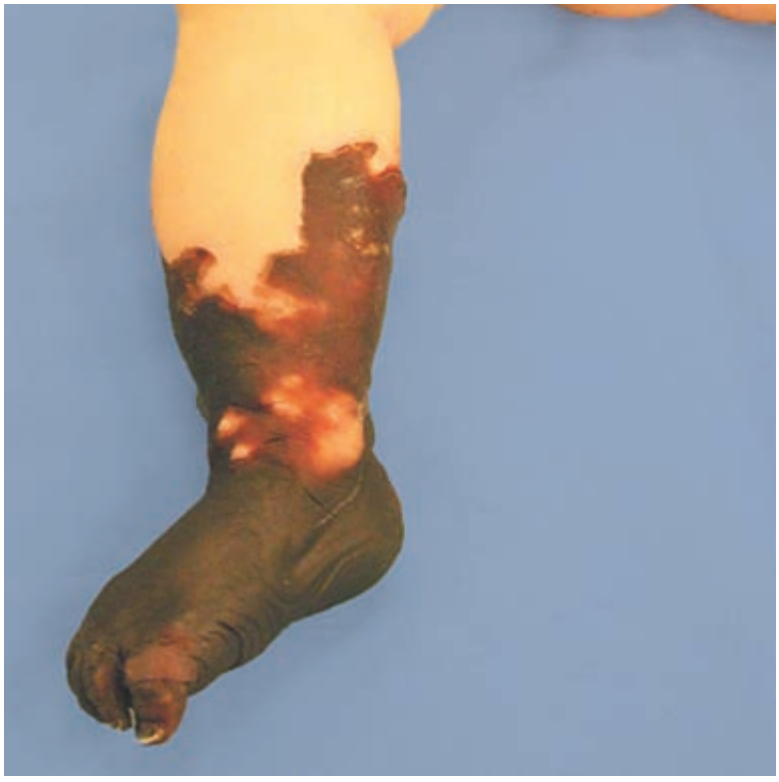


Figure 4. *Kawasaki disease: right lower extremity necrosis secondary to vasculitis.*

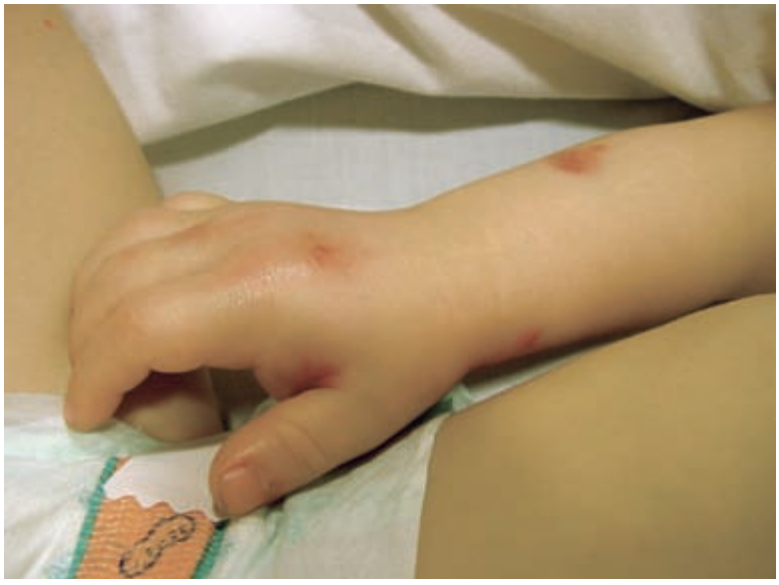


Figure 5. *Acute hemorrhagic edema of infancy: purpuric target-like lesions on right upper extremity and homolateral hand edema.*

Discussion

Vasculitis are rare in childhood. A 2002 British study shows an estimated global annual incidence of primary vasculitis in children under 17 years of age of 20.4/100,000, and HSP is most prevalent.[17] Although we cannot refer incidence data in our population, taking into account the average 1400 monthly consultations at our hospital pediatric Dermatology Section in the 2007-2008 period, and the total of 47 primary vasculitis in the 8-year period studied, we may infer a low incidence. As in the rest of publications, HSP was the most frequent vasculitis identified in our population.[18] HSP mainly affects the age group ranging from four to seven years. Fifty percent of cases occur in children under five, and 75 percent in children under ten years of age.[19] These data are consistent with our work results.

Fifty five percent of our patients had an infection at the time of diagnosis. The most frequently found etiologic agent was β-hemolytic *Streptococcus*, as referred in multiple reports.[20]

It is worth mentioning that we found references of 47 HSP cases in clinical records, but only 33 fulfilled EULAR/PReS diagnostic criteria; that is, 30 percent were overdiagnosed. This situation had previously been seen in other reports on HSP.[21] We believe it is caused by the use of non-thrombocytopenic purpura as sole HSP diagnostic criterion in children, following the criteria suggested by ACR and taken from the Chapel-Hill classification.[10-11,22] This would imply an unnecessary follow-up of patients for the likelihood of renal complication in HSP patients. Twenty to forty percent of HSP patients have renal symptoms appearing in 90 percent of the cases within one month

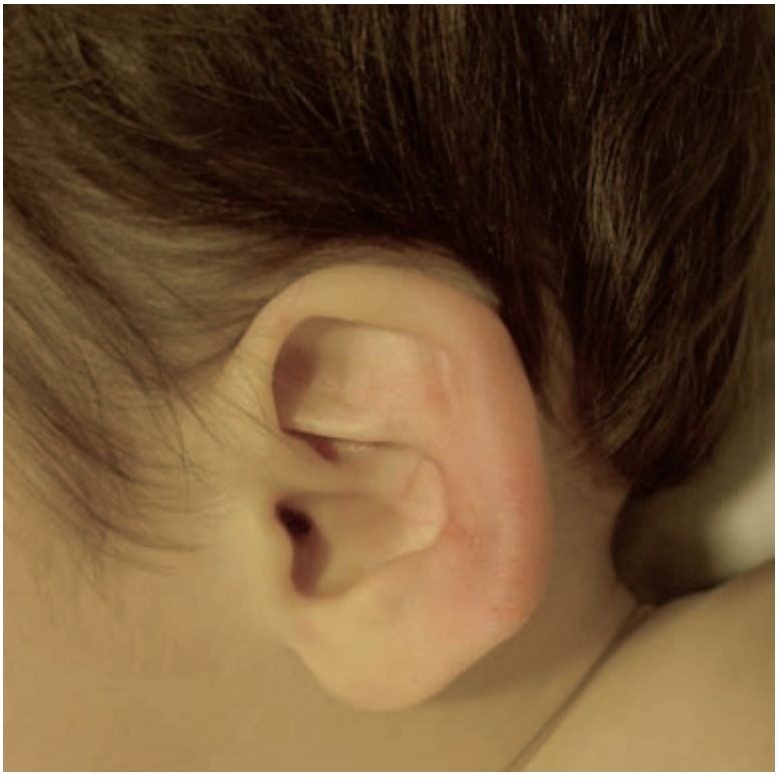


Figure 6. *Acute hemorrhagic edema of infancy: erythemato-purpuric lesion of left pinna.*

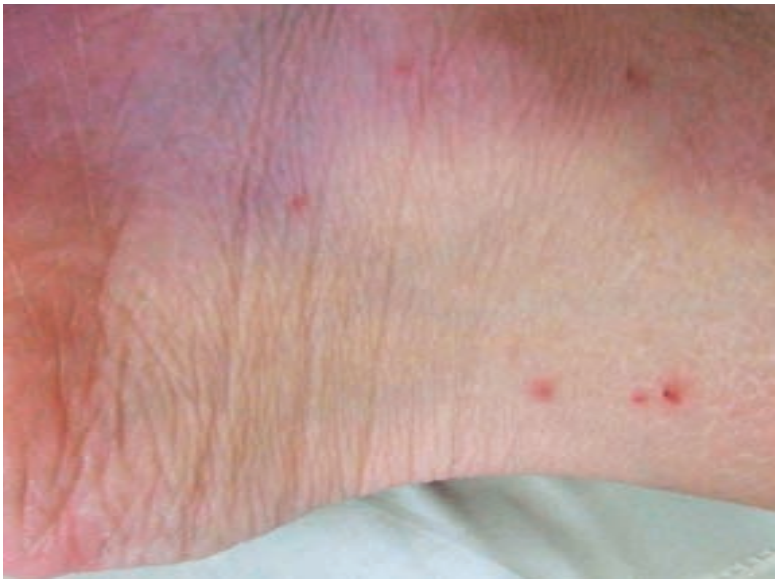


Figure 7. *Churg-Strauss syndrome: purpuric papules on lower extremities.*

of the onset of the disease. Generally, the outcome of patients with slight hematuria and proteinuria is good, while in less than 5 percent of the cases terminal renal disease occurs after a 10 to 25 years follow-up. Patients with nephritic or nephrotic syndrome have poorer prognosis.[23-25] We found a similar ratio of patients with renal alterations in our work (24 percent); however, none of our patients had long-term morbidity, which may be due to a shorter follow-up term so far.

In reference to KD, data found was similar to other national and international reports.[26-30] Due to the lack of a specific diagnosis test, the difficulty in differentiating it from other infectious or bacterial toxin-mediated diseases, and the large number of cutaneous-mucosal manifestations, the dermatologist has an important role in early diagnosis of this entity, allowing the institution of an early treatment and thus preventing cardiac and other organ sequelae.[30-33]

Coronary artery aneurysms appeared in 66 percent of our patients, and less frequently, myocarditis and pericarditis. These figures coincide with references in the literature.[34] Using the Takahashi score,[35] half of our patients showed certain clinical features such as persistent fever, thrombocytosis, less than one year of age and male gender, which enable prediction of high risk. A study by Juan et al. reaffirms these factors as cardiac risk predictors and adds delay in diagnosis.[33] All our one-year-old or younger patients (five cases) had cardiac involvement, one with another organ morbidity. The response of our patients to conventional KD treatment with intravenous immunoglobulin and aspirin was very good, with total resolution of coronary aneurysms in four cases, and partial resolution in two. None of them received corticosteroids as associated treatment.[36]

Eighty percent of reported AHEI cases occurred in 6 to 24-month-old children.[37] The ages of our patients were within this range. Also characteristic of AHEI is the good general condition of the children at the time of diagnosis and the history of a febrile event in 45 percent of the cases. Involvement disappears without sequelae after 2 to 60 days of evolution, mean 10 days.[15,38] Our three patients also behaved this way. We believe that not all AHEI cases were reported in our setting, because its frequency is usually three or four times below HSP, and our case material is much lower than this reference value.[39] Although less frequent, CPAN and CSS are differential diagnosis which must be considered in pediatric patients with palpable purpura; this work describes a case of each with classic clinical and histological manifestations.[40-46]

In conclusion, although pediatric vasculitis are rare, the dermatologist's role is essential to reach diagnosis, since cutaneous involvement is of great importance in diagnostic criteria; the presence of palpable purpura is mandatory to define HSP, and three of the diagnostic criteria are der-

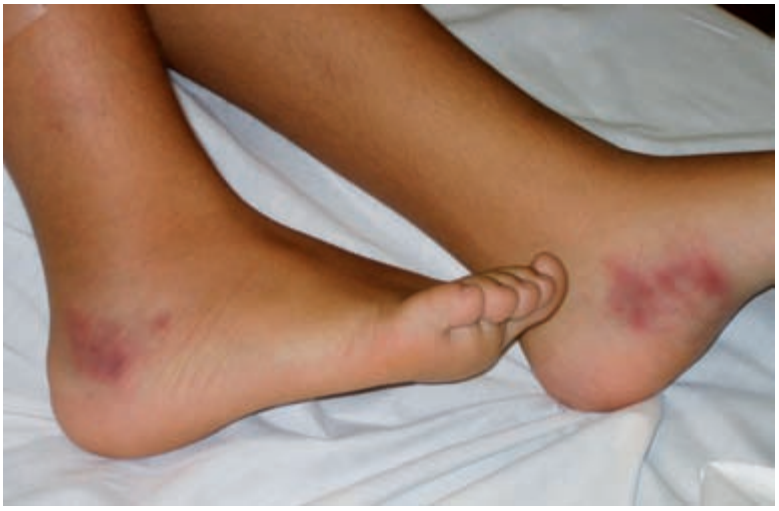


Figure 8. *Cutaneous nodose panarteritis: erythemato-purplish nodule on right ankle and left sole.*

matologic in KD. However, dermatologists are not always called to participate in diagnosis and treatment of these patients.

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