

# Revisiting clinical differences between hypersensitivity vasculitis and Henoch-Schönlein purpura in adults from a defined population

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Received on October 18, 2013; accepted in revised form on December 11, 2013.

Clin Exp Rheumatol 2014; 32 (Suppl. 82): S34-S40.

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**Key words:** cutaneous vasculitis, hypersensitivity vasculitis, Henoch-Schönlein purpura

**Funding:** this study was supported by a grant from "Fondo de Investigaciones Sanitarias" PI12/00193 (Spain). This work was also partially supported by RETICS Programs, RD08/0075 (RIER) and RD12/0009/0013 from "Instituto de Salud Carlos III" (ISCHII) (Spain).  
**Competing interests:** none declared.

## ABSTRACT

**Objective.** Hypersensitivity vasculitis (HV) and Henoch-Schönlein purpura (HSP) are the most common entities included within the category of cutaneous vasculitis (CV). Palpable purpura and histological changes characterised by the presence of leukocytoclastic vasculitis are common in both conditions. Therefore, considerable overlap between them is often seen. It is especially true when the CV occurs in adults. To further establish clinical differences between these two conditions, in the present study we assessed the main clinical differences between HV and HSP in a wide and unselected series of adults with CV from a defined population.

**Methods.** We reviewed the clinical records of 297 consecutive adults (age >20 years) seen at a single centre between January 1975 and December 2012 that were classified as having HSP or HV according to the criteria proposed by Michel et al. (J Rheumatol 1992; 19: 721-8).

**Results.** Based on the inclusion criteria, 102 adult patients (71 men/31 women) were classified as HSP and 195 (104 men/91 women) as HV. The mean age was similar in both groups (55.8±16.5 years in HSP and 56.8±18.3 years in HV). Precipitating events, usually an upper respiratory tract infection and/or drug intake, were more frequently observed in HV. Both at the beginning of the disease and when the CV was established clinical manifestations were more frequent in patients with HSP than in those with HV. It was the case for gastrointestinal (57.4% vs. 6.8%;  $p<0.001$ ), joint (51.5% vs. 36.6%;  $p=0.01$ ) and renal involvement (86.3% vs. 18.3%;  $p<0.001$ ). Corticosteroid (56.7% vs. 22%;  $p<0.001$ )

and cytotoxic drug (19.4% vs. 3.2%;  $p<0.001$ ) use was also more common in patients with HSP. After a median follow-up of 15.5 (interquartile range-IQR; 3-37) months in HSP and 4 (IQR; 2-12) months in HV, the outcome was better in HV than in HSP. In this regard, complete recovery (72.6% vs. 85.4%;  $p=0.01$ ) was more commonly observed in HV while residual renal involvement (15.3% vs. 4.2%;  $p<0.001$ ) was more common in HSP. The disease relapsed in 35.3% of patients with HSP and in 24.4% with HV ( $p=0.07$ ).

**Conclusion.** Our results confirm the claim that these two diseases presenting with similar cutaneous involvement are certainly two separate entities with greater systemic involvement and less favourable outcome in HSP.

## Introduction

Cutaneous vasculitis (CV) includes a wide and heterogeneous group of diseases that share a predominant involvement of the skin vessels. The main clinical manifestation of CV is a palpable purpura involving mainly the lower extremities. CV is characterised histologically by the presence of leukocytoclastic vasculitis (1-4).

Hypersensitivity vasculitis (HV) and Henoch-Schönlein purpura (HSP) are the most common entities included within the category of CV (1). While HV is a vasculitis observed generally in adults, HSP is the prototype of CV involving children (5, 6). HSP was initially considered a subtype of HV (7), but in 1990, a subcommittee of the American College of Rheumatology (ACR) established a series of criteria to define HSP and HV as two independent conditions (8-10). However, using these ACR criteria approximately one

third of patients met definitions for both HSP and HV simultaneously. In a further step, using the same database collected by the ACR subcommittee of vasculitis, Michel *et al.* established the criteria that best differentiate HSP from HV (11). Regrettably, in daily clinical practice, considerable overlap between these conditions is often present (6). It is especially true when the CV occurs in adults. Because of that, to further establish clinical differences between these two conditions, in the present study we assessed the main clinical differences between HV and HSP in a wide and unselected series of adults with CV from a defined population.

## Patients and methods

### Patients

We reviewed the clinical records of 297 consecutive adult patients (age  $\geq 20$  years) seen at a single centre between January 1975 and December 2012 that were classified as having HSP or HV according to the criteria proposed by Michel *et al.* (Table I) (11). As previously discussed, these criteria were based on the ACR database and methodology (10).

In keeping with former epidemiological studies on CV (2, 12-14), the majority of patients with suspected CV were sent to our hospital by general practitioners or they self-referred to the emergency unit. In most cases, consultation by dermatology staff physicians was usually requested. Patients with CV were screened for medications taken before and during the onset of the vasculitis, as well as for other data suggestive of systemic vasculitis or connective tissue diseases.

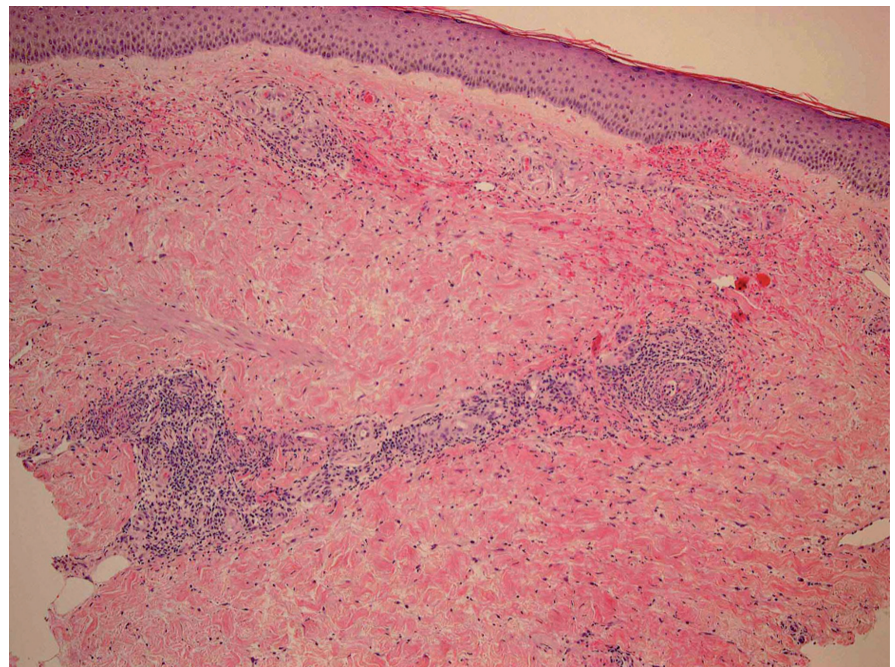
HSP and HV was pathologically confirmed in 83 and 150 cases respectively by a skin biopsy showing the characteristic histological findings consistent with leukocytoclastic vasculitis, including neutrophilic infiltration, leukocytoclasia, and fibrinoid necrosis into the vessel wall of arterioles, capillaries, and post-capillary venules, and red cell extravasation (15, 16) (Fig. 1). The remaining patients without skin biopsy had typical non thrombocytopenic symmetric palpable purpura (Fig. 2). In addition, all of them fulfilled the cri-

**Table I.** Criteria to differentiate Henoch-Schönlein purpura from hypersensitivity vasculitis (Traditional Format)\*.

Criterion	Definition
1. Palpable purpura	Slightly elevated purpuric rash over one or more areas of the skin not related to thrombocytopenia.
2. Bowel angina	Diffuse abdominal pain worse after meals or bowel ischaemia usually including bloody diarrhoea.
3. Gastrointestinal bleeding	Gastrointestinal bleeding, including melena, hematochezia or positive test for occult blood in the stool.
4. Haematuria	Gross haematuria or microhaematuria.
5. Age at onset $\leq 20$ years	Development of first symptoms at age 20 or less.
6. No medications	Absence of any medications at onset of disease which may have been a precipitating factor.

The presence of any three or more of the 6 criteria yields a correct classification of HSP cases of 87.1%.

\*Data reported by Michel *et al.* (31). *J Rheumatol* 1992; 19: 721-8.



**Fig. 1.** Skin biopsy of a patient with cutaneous vasculitis. Typical histological findings consistent with leukocytoclastic vasculitis including neutrophilic infiltration, leukocytoclasia, fibrinoid necrosis, and erythrocyte extravasation into the vessel wall of arterioles, capillaries, and postcapillary venules from dermis are observed.

teria proposed by Michel *et al.* for HV or HSP (11).

### Clinical definitions

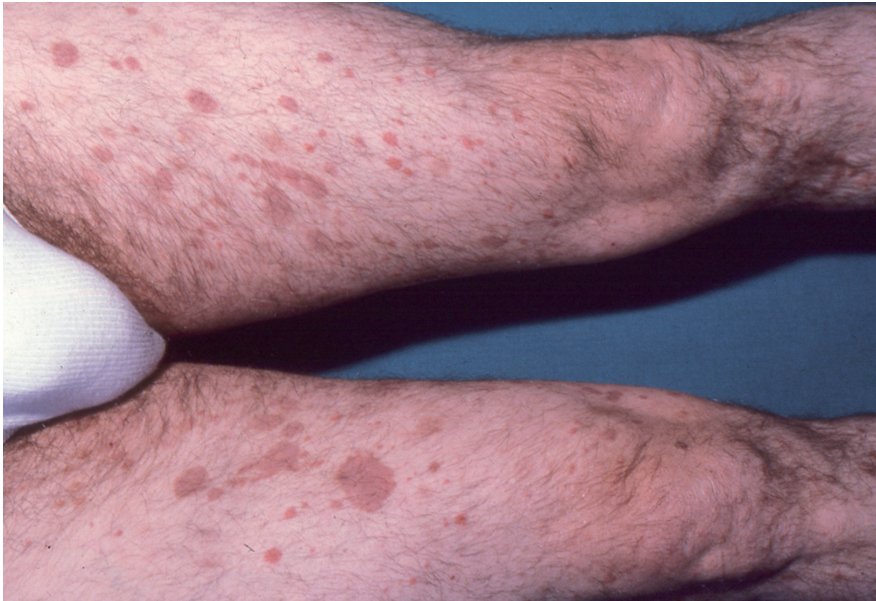
1) Classification by age groups: patients older than 20 years were considered as adults and those aged  $\leq 20$  as children. The cut-off age of 20 years was chosen because this age was proposed as a criterion for HSP by the ACR (10) and because this age best discriminated HSP from HV in previous studies (1, 10, 11, 12, 17).

2) Precipitating events: a drug or a mild infectious process (mostly an upper respiratory tract infection-URTI) were considered as the probable precipitating event of a CV if they occurred closely (within the preceding week) to the onset of the skin lesions.

3) Fever was defined as a temperature  $>37.7^{\circ}\text{C}$ .

4) Joint symptoms included arthralgia with or without joint effusion (arthritis).

5) Nephropathy was categorised as mild or severe (4). Mild nephropathy



**Fig. 2.** Typical non-thrombocytopenic purpura palpable in the lower extremities of a patient with hypersensitivity vasculitis.

included those patients with microhaematuria ( $\geq 5$  red cell/hpf) and/or proteinuria that did not reach the nephrotic range. A patient was included in the category of severe nephropathy if he/she had: a) nephrotic syndrome, defined as a plasma albumin levels  $\leq 25$  gm/liter and either 1 gm of proteinuria/day/m<sup>2</sup> of body surface area in children, or  $>3.5$  gm of proteinuria/day in adults, with or without oedema; or b) when there was an acute nephritic syndrome defined as haematuria with at least 2 of the following abnormalities: hypertension, increased plasma urea or creatinine levels, and oliguria. Renal insufficiency was considered to be present if the plasma creatinine was  $>125\%$  of the upper limit of normal.

6) Gastrointestinal manifestations included either bowel angina (diffuse abdominal pain worsening after meals) or gastrointestinal bleeding (melena, hematochezia, or positive stool Guaiac test).

7) Constitutional syndrome was defined as asthenia and/or anorexia and weight loss of at least 4 kg

8) Renal sequelae were defined if at last follow-up there was persistent renal damage manifested by haematuria, proteinuria or impairment of renal function.

9) A relapse was considered to be present when a patient previously diagnosed with HSP or HV and asymptomatic for at least one month, presented

again a new flare of cutaneous lesions or other systemic complications (17).

#### Clinical study

Besides a complete history and physical examination, the following tests were performed routinely in most patients: Complete blood cell count, Westergren erythrocyte sedimentation rate (ESR)/1<sup>st</sup> hour, and routine urinalysis. In addition, an immunological profile including rheumatoid factor (RF) (performed initially by quantitative Latex agglutination test, and later on by nephelometry), antinuclear antibodies (ANAs) (by indirect immunofluorescence initially using rodent tissues as substrate or more recently using Hep-2 cells) and serum levels of C3 and C4 (firstly by radial immunodiffusion and more recently by nephelometry) were performed to most adults with HSP. Anti-neutrophil cytoplasmic antibodies (ANCA) were performed in patients who had been diagnosed since 1992. They were initially performed by indirect immunofluorescence on alcohol fixed neutrophils and later on, by ELISA with purified proteinase-3 and myeloperoxidase. Other determinations were cryoglobulins (the composition of the cryoprecipitate was determined by double immunodiffusion with specific antibodies) and immunoglobulins determined by nephelometry. Additional

tests such as anti-DNA antibodies (by immunofluorescence with *Chrythidia luciliae* as substrate), blood cultures, Guaiac test for occult blood, serology for hepatitis B, or C or HIV infection, were performed only when it was considered to be indicated according to the clinical practice. Anaemia was defined as a haemoglobin level  $\leq 110$  g/L. Leukocytosis as a white blood cell count  $\geq 11 \times 10^9$ /L. The ESR was considered to be increased when it was higher than 20 or 25 mm /1<sup>st</sup> hour for men or women, respectively (17, 18). Increased IgA levels were defined as total IgA level  $>400$  mg/dl.

A skin biopsy was performed in most adults with skin. Renal biopsy was usually performed if there were signs suggestive of severe renal disease, such as protein excretion above 1 g/day, an elevated plasma creatinine concentration or arterial hypertension.

Therapy, follow-up, possible relapses and the final outcome were assessed in all the patients.

#### Data collection

##### and statistical analysis

Data were first reviewed and then analysed in an attempt to retrieve the following information: etiologic, clinical, laboratory and pathologic features, treatment and prognosis. Clinical, laboratory and pathological data were extracted from their clinical records according to a specifically designed protocol, reviewed for confirmation of the diagnosis, and stored in a computerised file. To minimise entry error, all the data were double checked.

The statistical analysis was performed with the STATISTICA software package (StatSoft Inc. Tulsa, OK, USA). Results were expressed as mean  $\pm$ SD (standard deviation) for variables with a normal distribution or as median and range or interquartile range (IQR) (25<sup>th</sup>, 75<sup>th</sup>) for those not normally distributed. Continuous variables (normally and not normally distributed) were compared with the 2-tailed Student's *t*-test or the Mann-Whitney U-test, respectively. The chi-square test or the Fisher exact test was used for the dichotomous variables. Statistical significance was considered as *p*-value  $<0.05$ .

## Results

Based on the inclusion criteria described above 102 adult patients (71 men/31 women) were classified as having HSP and 195 (104 men/91 women) as HV. The main demographic and etiologic factors are summarised in Table II.

### Demographic data and etiological factors

The mean age at the onset of CV was similar in both groups. It was  $55.8 \pm 16.5$  years (range, 20.5–87.2) in patients classified as having HSP and  $56.8 \pm 18.3$  years (range, 20.1–95.4) in those that fulfilled classification criteria for HV ( $p=0.6$ ). Both entities were more common in men and occurred more commonly in fall. At disease onset, 16.7% of HSP and 49.2% of HV ( $p<0.001$ ) were taking drugs, most of them for an URTI.  $\beta$ -Lactam antibiotics were the medication more commonly prescribed. Hepatitis virus infection was only found in 3 HSP (2 type B and 1 type C) and in 8 HV patients (2 type B and 6 type C). All patients were negative to HIV test.

### Clinical features

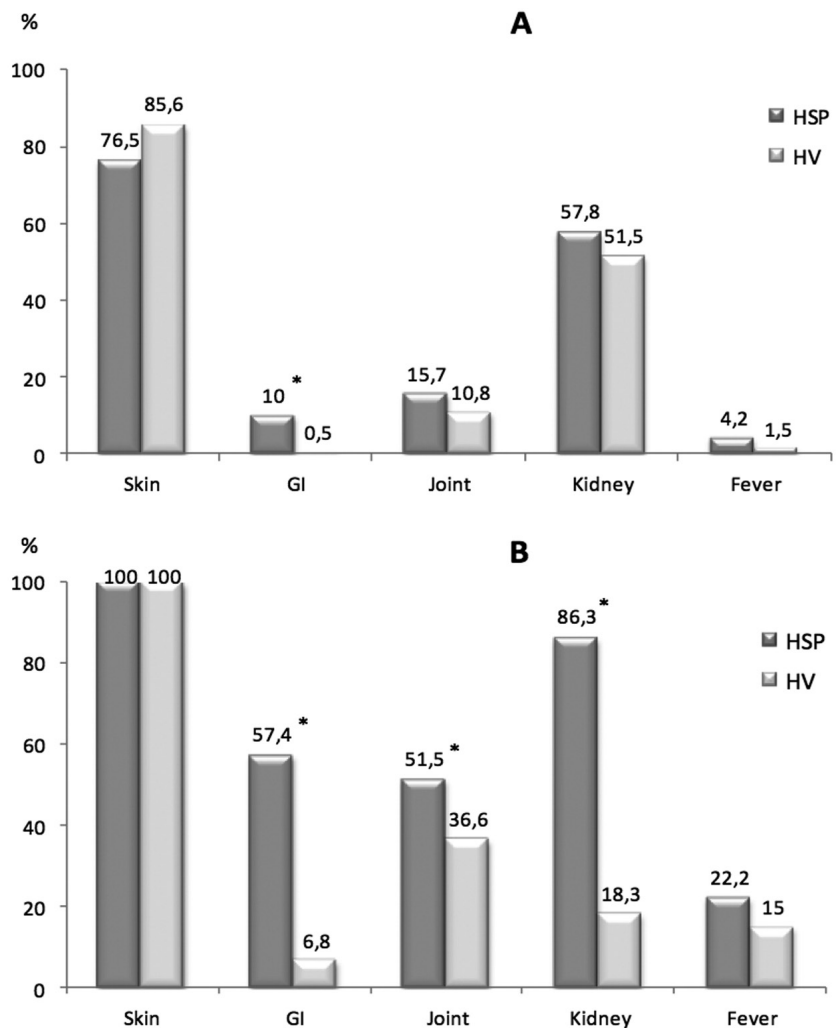
The main clinical features are summarised in Figure 3. At the onset of the disease a comparative analysis showed the following differences between HSP and HV: skin lesions (76.5% in HSP vs. 85.6% in HV;  $p=0.06$ ), gastrointestinal involvement (10% in HSP vs. 0.5% in HV;  $p<0.001$ ), joint symptoms (15.7% in HSP vs. 10.8% in HV;  $p=0.3$ ), nephropathy (57.8% in HSP vs. 51.5% in HV;  $p=0.5$ ) and fever (4.2% in HSP vs. 1.5% in HV;  $p=0.2$ ).

During the clinical course of the disease, cutaneous lesions were observed in 100% of the cases. Palpable purpura, was present in 100% of patients with HSP and in 95% of those with HV ( $p=0.03$ ). Other skin lesions, such as ulcers or blisters, were observed in a 23.7% of patients with HSP and 24.2% of patients with HV ( $p=0.9$ ). In both entities skin lesions were more common in the lower extremities, although the upper extremities and trunk were also involved. The median duration of the skin lesions was 10 (IQR 7–15) days in HSP and 10 (IQR 6–15) in HV ( $p=0.4$ ).

**Table II.** Main demographic and etiologic features of patients with Henoch-Schönlein purpura (HSP) and hypersensitivity vasculitis (HV).

	HSP	HV	p-value
Number of patients	102	195	
Mean age $\pm$ SD (years)	$55.8 \pm 16.5$	$56.8 \pm 18.3$	$p=0.6$
Sex (men/women) n; %	71/31; 69.6/30.4%	104/91; 53.3/46.7%	$p<0.01$
Seasonal pattern, %			
Spring	26.5%	24.6%	$p=0.7$
Winter	28.4%	25.6%	$p=0.6$
Fall	27.4%	23.6%	$p=0.5$
Summer	16.7%	24.6%	$p=0.1$
Etiological factors, no. (%)	29 (28.4%)	119 (61%)	$p<0.01$
Infections	23 (22.5%)	69 (35.4%)	$p=0.02$
URTI*	14 (14%)	37 (19.4%)	$p=0.25$
Hepatitis virus infection			
HBV	2 (2.8%)	2 (1.5%)	$p=0.5$
HCV	1 (2.7%)	6 (8.8%)	$p=0.2$
Drugs at disease onset	17 (16.7%)	96 (49.2%)	$p<0.01$
$\beta$ -lactam antibiotics	7 (43.7%)	24 (25%)	$p=0.12$
Analgesics/NSAIDs	3 (20%)	21 (21.8%)	$p=0.86$
Others	6 (37.5%)	53 (55.2%)	$p=0.2$

\*URTI: upper respiratory tract infection. NSAIDs: non-steroidal anti-inflammatory drugs.



**Fig. 3.** Main clinical features of 102 adult patients with Henoch-Schönlein purpura (HSP) and 195 with hypersensitivity vasculitis (HV), at disease onset (A) and when the disease was fully established (B). \* $p<0.05$ ; GI: gastrointestinal.

Gastrointestinal involvement was more frequent in HSP (57.4% vs. 6.8% in HV;  $p<0.001$ ). The main symptom was the typical colicky abdominal pain that was also significantly more common in patients with HSP (57.4% in HSP vs. 4.7% in HV;  $p<0.001$ ). Other gastrointestinal manifestations such as nausea and/or vomiting (21% vs. 2%;  $p<0.001$ ) and melena/rectorrhagia (26% vs. 4%;  $p<0.001$ ) were also more frequent in HSP. Stool Guaiac test was positive in 47.5% (19 of 40 tested) of HSP patients and in 6.8% of those with HV (3 of 44 tested) ( $p<0.001$ ).

Joint manifestations (arthralgia and/or arthritis) and joint swelling on physical examination occurred more frequently in HSP than HV (51.5% vs. 36.6% in HV;  $p=0.01$ , and 28.7% vs. 18% in HV;  $p=0.03$ , respectively). The most frequent joint pattern observed was a non-erosive oligoarthritis affecting the ankles and/or knees.

Renal involvement was also more common in HSP than in HV (86.3% vs. 18.3%;  $p<0.001$ ). Nephrotic syndrome (14% vs. 4%;  $p=0.007$ ) and nephritic syndrome (11.3% vs. 1.4%;  $p=0.001$ ) were also more frequent in HSP. Serum creatinine (mg/dl) was somewhat higher in HSP (median; IQR) (1.3; 1–2.2 vs. 1.2; 0.9–1.7 in HV) ( $p=0.2$ ).

#### Laboratory data

The main laboratory findings are summarised in Table III. Routine laboratory tests were done in all the patients at the time of diagnosis. Anaemia was present in 10.8% of patients with HSP and in 9.4% of patients with HV ( $p=0.7$ ). Leukocytosis was more common in HSP than in HV (24.2% vs. 19.4%;  $p=0.3$ ). The mean ESR was similarly increased in HSP ( $47.9\pm 29.5$  mm /1<sup>st</sup> hour) and HV ( $46.8\pm 26.7$  mm /1<sup>st</sup> hour) ( $p=0.8$ ). Serum IgA levels were increased in 54.8% (17 of 31 tested) of patients with HSP and in 48.9% (22 of 45) of those with HV ( $p=0.6$ ). The mean $\pm$ SD value of IgA was similar in both conditions (HSP:  $452.7\pm 208.4$  mg/dl; HV:  $432.3\pm 282.5$ ) ( $p=0.73$ ). Other immunologic tests such as RF, and ANAs were generally negative in both groups and in the few patients in whom they were positive they were at low titer and other

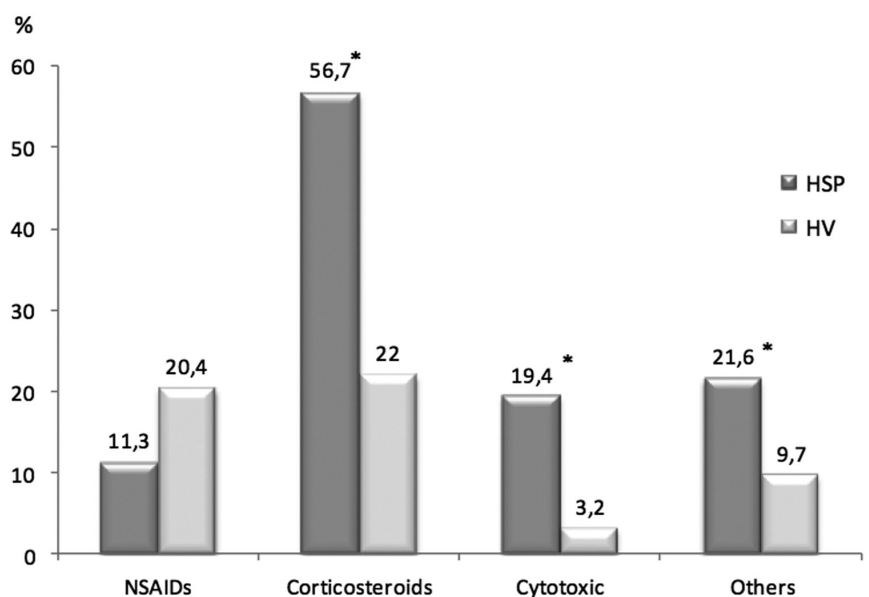
**Table III.** Routine and immunologic laboratory findings in patients with Henoch-Schönlein purpura (HSP) and hypersensitivity vasculitis (HV).

	HSP (n=102)	HV (n=195)	p-value
Leukocytosis	24.2% (22/91)	19.4% (37/191)	$p=0.3$
Anaemia	10.8% (11/102)	9.4% (18/192)	$p=0.7$
Increased ESR	83% (49/59)	84.4% (92/109)	$p=0.8$
Increased IgA serum levels	54.8% (17/31)	48.9% (22/45)	$p=0.6$
Positive Rheumatoid Factor	7.3% (6/82)	19.7% (30/152)	$p=0.01$
Positive Antinuclear antibodies	19.5% (17/87)	21.6% (33/153)	$p=0.7$
Positive ANCA	0% (0/40)	3% (2/65)	$p=0.3$
Cryoglobulins	20% (14/70)	22.7% (27/119)	$p=0.7$
Low C3 and/or C4	9.6% (8/83)	4.9% (7/143)	$p=0.16$

Routine laboratory tests were performed to all of the patients at the time of diagnosis.

Values are percentages (no. positive/total no. tested).

Leukocytosis was defined as a leukocyte count  $\geq 11 \times 10^9$ /liter, anaemia as haemoglobin  $< 110$  gm/liter, elevated erythrocyte sedimentation rate (ESR) if it was higher than 20 or 25 mm/1<sup>st</sup> hour for men or women respectively, and increased IgA levels if total IgA level was  $> 400$  mg/dl.



**Fig. 4.** Treatment of 102 adult patients with Henoch-Schönlein purpura (HSP) and 195 with hypersensitivity vasculitis (HV).

\* $p<0.05$ . NSAIDs: non-steroidal anti-inflammatory drugs.

diseases such as rheumatoid arthritis, systemic lupus erythematosus or other connective tissue disease were excluded. In patients with cryoglobulins the precipitate was scarce (+/+++ or trace amounts), and none of them could be classified as having cryoglobulinaemic vasculitis. ANCA were negative in all patients with HSP and it was positive in only 2 patients with HV ( $p=0.3$ ) (1 pANCA and 1 undetermined, in both cases at low titer and without fulfilling definitions for primary systemic necrotising vasculitis).

#### Treatment and outcome

Corticosteroids and cytotoxic drugs

were the usual therapy for both diseases. Corticosteroids were prescribed because of persistent skin lesions or visceral involvement such as severe abdominal pain, gastrointestinal bleeding or nephropathy. Cytotoxic drugs were prescribed either as corticosteroid-sparing agents or as additional therapy in patients with severe renal involvement. When we specifically assessed corticosteroid and immunosuppressive drug use in patients with HSP and HV, we observed that they were more frequently used in patients with HSP (Fig. 4): corticosteroids (56.7% in HSP vs. 22% in HV;  $p<0.001$ ) and cytotoxic drugs (19.4% in HSP vs. 3.2% in HV;  $p<0.001$ ).

The following cytotoxic drugs were used in HSP (azathioprine in 8 patients, cyclophosphamide in 8, mycophenolate mofetil in 1, chloroquine in 1, and azathioprine plus mycophenolate mofetil in 1 patient) and HV (azathioprine in 2 patients, cyclophosphamide in 2, methotrexate in 1, and mycophenolate mofetil plus cyclosporine in 1 patient).

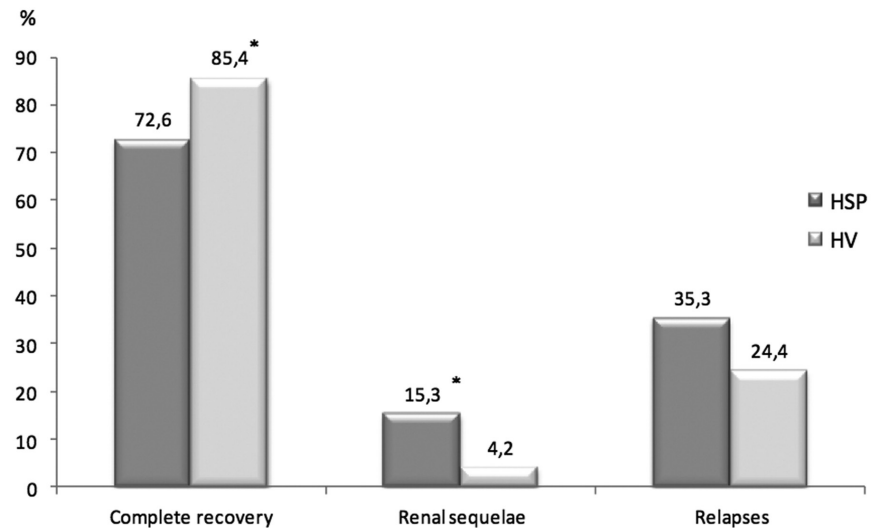
Duration of treatment in months was higher in patients with HSP (median 3 months (IQR 1-12) than in those with HV (median 1 (IQR 1-3) in HV) ( $p=0.02$ ).

Infections secondary to treatment were only observed in 5 patients with HSP (pneumonia in 4 and herpes zoster in a single case) and in 2 patients with HV (1 pneumonia and 1 upper respiratory tract infection). Apart from 1 patient with pneumonia that died, the rest of patients experienced full recovery following antibiotic therapy or antiviral therapy in the case of herpes zoster.

After a median follow-up of 15.5 (IQR; 3-37) months in HSP and 4 (IQR; 2-12) months in HV, the outcome was better in HV than in HSP (Fig. 5). Complete recovery was more frequently observed in HV (85.4% vs. 72.6% in HSP;  $p=0.01$ ). Renal sequelae were more commonly observed in patients with HSP than in those with HV (15.3% in HSP vs. 4.2% in HV;  $p<0.001$ ). The disease relapsed in 35.3% of patients with HSP and in 24.4% of patients with HV ( $p=0.07$ ).

## Discussion

HV and HSP are considered two related entities included within the wide group of CV. They share many clinical and pathological features. This fact led in some cases to a misdiagnosis because of frequent overlapping. Due to this, based on the same database collected by the ACR, Michel *et al.* (11) proposed a new set of criteria to differentiate HV from HSP. In the present study we have applied these criteria to a large series of unselected adult patients with CV that fulfilled the ACR classification criteria for HV or HSP (9, 10). In an attempt to minimise selection bias, unlike other studies in which patients were recruited from a single service, we included all HSP or



**Fig. 5.** Outcome of 102 adult patients with Henoch-Schönlein purpura (HSP) and 195 with hypersensitivity vasculitis (HV). \* $p<0.05$ .

HV patients seen at the Rheumatology, Nephrology, Dermatology and Internal Medicine Departments of our center. Since in some patients a skin biopsy is not performed, especially in those patients with a mild vasculitic syndrome presenting with typical non thrombocytopenic palpable purpura, to reduce the risk of potential selection based on disease severity, in the present study we included all the patients aged >20 years diagnosed as having HV or HSP in our center, regardless of whether a biopsy was carried out or not.

Due to the considerable overlap between HV and HSP, in particular when the ACR-1990 classification criteria are applied (10), to discriminate HSP from HV we used the criteria put forward by Michel *et al.* (11). Following this procedure, patients from our series who only presented palpable purpura without other clinical features were classified as HV.

In a previous study conducted to establish differences between HV and HSP in adults, García-Porrúa and González-Gay reported more severe gastrointestinal symptoms, increased risk of renal complications and more severe relapses in those with HSP (12). As observed in our series, patients with HV often have a history of drug exposure shortly before the onset of the CV (19). However, the outcome of patients with HV is generally good, and in many cases they have a benign process limited to skin (20, 21).

Although we could not observe significant differences in the age of onset between adults with HV and HSP in our series, in keeping with former studies (11, 12), systemic involvement, need of treatment and outcome differed between HSP and HV patients. Therefore, we confirmed a higher frequency of gastrointestinal and joint manifestation as well as more common renal involvement in patients with HSP. In line with the presence of a more severe disease, our patients with HSP received more commonly corticosteroids and immunosuppressive drugs than those with HV.

The reasons for the differences between these two conditions that clinically show a similar cutaneous involvement but a different systemic expression are unknown. Several authors have confirmed the potential implication of an aberrant glycosylation of the hinge region of IgA1 in the pathogenesis of HSP (22-24). Although HV and HSP are characterised by infiltration of the small blood vessels by polymorphonuclear leukocytes and the presence of leukocytoclasia, in typical cases of HSP direct immunofluorescence may reveal the presence of IgA-dominant immune deposits in the walls of the small vessels. However, in the study reported by Michel *et al.* there was no difference in the frequency of elevation of IgA serum levels between patients with HSP and HV. This lack of significant differences

in serum IgA levels was also observed in our series.

A plausible explanation for the differences between these two closely related conditions may be a different genetic component. In this regard, an association of disease susceptibility with several gene polymorphisms has been found in HSP (25, 26). It does not seem to be the case for patients with HV. With respect to this, HSP and HV patients exhibit a different *HLA-DRB1*\* pattern of association with a higher risk to develop HSP in individuals carrying the *HLA-B\*01* allele. Also, cytokine polymorphisms such as those located in the interleukin 1 receptor antagonist gene have been associated with the presence of severe renal involvement in patients with primary cutaneous vasculitis classified as having HSP but not in those with HV (27).

In conclusion, our results confirm the claim that these two diseases presenting with similar cutaneous involvement are certainly two separate entities with greater systemic involvement and less favourable outcome in HSP. Based on our clinical experience, the absence of a previous history of drug exposure in a patient presenting with CV and gastrointestinal manifestations or nephritis should alert us on the presence of HSP rather than HV.

### Acknowledgments

The authors thank the members of the Rheumatology, Dermatology, Paediatrics, and Pathology Services of Hospital Universitario Marqués de Valdecilla, Santander, Spain

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