Demographic and clinical features of pediatric vasculitis: a single-center study

Trindade TS[1], Morais CG[2], Maia A[2], Rodrigues M[3], Brito I[3]

[1] Faculty of Medicine of the University of Porto, Centro Hospitalar e Universitário de São João
ORCID: ORCID 0000-0003-3000-649X

[2] Pediatrics Department, UAG-MC, Centro Hospitalar e Universitário de São João

[3] Unidade de Reumatologia Pediátrica e Jovem Adulto, Centro Hospitalar e Universitário de São João

Correspondence to

Tiago Santos Trindade

E-mail: up201603178@up.pt

Submitted: 07/10/2022

Accepted: 25/01/2023

Abstract

Introduction: Vasculitides are rare systemic conditions which may occur in childhood. This study aims to document demographic and clinical features of systemic vasculitides in a tertiary center, comparing our outcomes with previously published studies of other international centers.

Methods: Patients presenting with systemic vasculitis before 18 years of age, admitted to a tertiary Portuguese center at diagnosis or during follow-up, from 2009 to 2020, were retrospectively included in this study.

Results: In our study, we included 138 patients. The youngest patients at diagnosis were in the Kawasaki's disease (KD) group, with a median age at diagnosis of 2.26 years old (IQR 1.07-6.20), as opposed to the Behçet's syndrome (BS) group with a median age at diagnosis of 13.41 years old (IQR 10.19-16.75), which was significantly higher ($p<0.05$). Gender ratio was only higher in females in the BS group; however, there was no significant difference between groups. Cutaneous involvement was > 90% in both IgA Vasculitis (IgAV) and KD. Gastrointestinal symptoms were common in all groups (15-50%), rarer in BS (17%). Arthritis and arthralgia were highly prevalent in IgAV (65%). The American Heart Association criteria of diagnosis for complete KD were met in 62% of cases. No significant difference was found in age distribution between complete and incomplete diagnosis ($p=0.616$). Mean duration of fever in KD was 9.6 ±2.1 days, which was higher than anticipated. Renal manifestations in IgAV (11%) and ophthalmic involvement in BS (22%) were lower than expected. There was a notable number of children reporting joint involvement in KD (27%). We also noticed a slightly higher prevalence of vascular events in BS (30%).

Conclusions: Each specific vasculitis assessed had different key symptoms, but there are several complaints and signs shown by our patients, some of them overlapping between vasculitides and others very atypical, such as recurrent epididymitis in BS due to microvasculitis. We can state that most of our findings are in concordance with current literature, with some notable exceptions. Pediatric multicentric population-based studies are warranted to increase research and design clinical trials concerning this field of knowledge.

Keywords: Vasculitis; Systemic Vasculitis; IgA Vasculitis; Mucocutaneous Lymph Node Syndrome; Behçet Syndrome.

Key messages

- Arthralgia and arthritis symptoms are common in patients diagnosed with Kawasaki's disease and need to be addressed properly.
- Physicians need to pay careful attention to vascular events arising in Portuguese pediatric patients with Behçet's Syndrome.
- Deficit of Adenosine deaminase 2 should be considered in children with diagnosis criteria for Polyarteritis Nodosa.

Introduction

Vasculitides are a group of rare clinical conditions caused by inflammation of blood vessels. In the pediatric setting, these can be challenging to physicians, often presenting with nonspecific symptoms[1,2].

The size of the vessels, the extent of the lesions and the sites affected are some of the factors explaining the variable, multisystemic symptoms referred by patients. A multidisciplinary approach is usually required to guarantee a full recovery[1]. IgA Vasculitis (IgAV), formerly known as Henoch-Schönlein Purpura, is the most common vasculitis in children. Kawasaki disease (KD) is also a frequent vasculitis, but its prevalence differs according to ethnicity, higher in Oriental populations[3]. Other vasculitides, such as the large vessel affecting Takayasu arteritis (TA), the medium vessel Polyarteritis Nodosa (PAN), the small vessel ANCA-associated or ANCA-negative vasculitis and variable vessel Behçet's syndrome (BS) also occur in pediatric patients. Giant cell arteritis is rarer[2].

Even though IgAV typically displays a self-limited course with little to no further complications, that does not occur in other less frequent subtypes of vasculitis[4,5]. KD has a well-known tropism to coronary arteries, therefore early identification and treatment is of paramount importance to reduce aneurysms which can lead to severe outcomes and even death.[6] BS usually appears in the second and third decades of life and takes on a chronic course of remission and relapsing.[3] Disease severity usually improves with age[7]. Two factors which seem to contribute to a more severe prognosis are male gender and younger age at disease onset, hence early recognition and referral to a specialized center are fundamental[8,9].

Since pathogenesis and molecular mechanisms are not yet fully understood in most vasculitides, standardized criteria are necessary to clearly establish a routine management and

to include groups of patients in clinical trials.[10] Several classification criteria have been proposed and validated throughout the years. Even though their usage is mostly intended for research purposes, physicians often apply these criteria as diagnostic aid tools[4,5].

In the last decade, there has been an increase in published demographic data regarding vasculitides. Most studies focus on adult populations where these conditions are more common. There are fewer pediatric studies regarding the less frequent BS, PAN, and TA, and most have small sample sizes which limits the interpretation of results. Vasculitides in children have different characteristics than vasculitides in adults and need to be addressed separately[2]. This brought to our attention the need for studies to be held with a greater number of pediatric patients, for correct clinical and demographic assessment.

In this single-center study, we sought to document the clinical and demographic characteristics of systemic vasculitides diagnosed in pediatric ages, resorting to reported data in a tertiary Portuguese center. We characterized the genre and age distribution of each vasculitis, assessed for the fulfillment of the classification criteria, and compared our outcomes with previously published studies of other international centers.

Patients and Methods

Patients presenting with vasculitis associated symptoms before 18 years of age, admitted to our tertiary center at diagnosis or during follow-up, from 2009 to 2020, were retrospectively included in this study. The classification criteria of vasculitis are displayed in Table 1. We decided to include all patients with a final clinical diagnosis of systemic vasculitis; some do not fulfill classification criteria in Table I.[11–14] All patients were evaluated by experienced pediatric rheumatologists. Data was collected from electronic records by several methods: by searching for coded diagnosis, for keywords in clinical registries, and in the center's Pediatric and Young Adult Rheumatology Unit's database. Every case was then analyzed to ascertain for inclusion and exclusion.

Variable selection

All patients in the study were assessed for demographics, including age at diagnosis, genre, ethnicity, and nationality. Selection of symptoms to assess in each specific vasculitis was performed by combining the most relevant and frequent symptoms, based on the diagnostic criteria, evidence in literature and clinical experience.[11–14] Symptoms assessed in each vasculitis are presented in Table I.

Exclusions and Bias

Transferred patients missing data from the primary evaluation at another hospital were excluded. The same method of data collection was used for all patients. The study design allowed an adequate follow-up period of at least one year.

Statistical Analysis

Data collection and statistical analysis were performed using Microsoft® Excel® (2022) and IBM SPSS® statistics 26. Categorical variables were described as absolute and relative frequencies, continuous variables with symmetric distribution by mean (±standard deviation) and continuous variables with asymmetric distribution by median with interquartile range (IQR).

The difference in age at onset between groups was analyzed by performing a non-parametric Kruskal-Wallis One-Way ANOVA test for skewed samples. A Two Proportion Z-Test was performed to analyze the difference between gender among the different groups. The difference in age at onset between complete and incomplete KD was tested by running a Mann-Whitney U Test. A value of $p<0.05$ was considered significant.

Ethics

The present study was approved by the Ethics Committee of our hospital. Access to the collected database were limited to the authors. No information was included that could disclose the identity of any patient included.

Results

A total of 138 patients were enrolled. The median age of onset was 6.05 years (IQR 3.40-9.02). KD had the youngest patients with a median age of 2.26 years (IQR 1.07-6.20), followed by PAN (5.38±3.33 years) and IgAV (6.02 years; IQR 4.48-8.16). However, patients diagnosed with BS had a median age of 13.41 years (IQR 10.19-16.75), which was significantly higher than the children in the IgAV and KD groups (Table S1).

Female predominance was only observed in BS, with a male to female ratio of 0.64:1 (IgAV – 1.31:1; KD - 1.85:1; PAN – 2:1). However, there was no significant difference between groups (Table S2). Most patients in all groups were Portuguese and Caucasians. Further details are shown in Table II.

Cutaneous involvement was the most common, found in 87.7% of patients. In the groups referring to IgAV and KD, nearly all patients presented with cutaneous symptoms (100% and 94.6%, respectively), higher than the 43.5% of patients in BS's group. Gastrointestinal symptoms were found in 40.2% of patients, also more common in patients reporting with either IgAV or KD (41.9% and 48.6%, respectively).

Ophthalmic involvement (24.8%) was highly variable between groups. KD group had a high prevalence (70.3%), with these patients reporting the characteristic bilateral conjunctivitis. 21.7% of patients with BS also presented with ophthalmic symptoms, the most common being panuveitis. These symptoms were rarer in IgAV (0,03%).

Joint involvement was seen as either arthritis or arthralgia in 46.4% of patients. The majority was seen in the IgAV group (64.9%), less frequent in both KD and BS' groups (27.0% and 26.1%, respectively). Patients in the PAN and Takayasu group all presented cardiovascular findings as well as 16.2% of patients with KD. Summarized data can be found in Figure 1.

IgA Vasculitis

Seventy-seven patients were included (Table 3) and three were excluded due to missing data regarding clinical presentation. All patients presented with a raised, palpable skin rash (purpura). Less than half of the patients presented gastrointestinal symptoms (41.9%); the most common

were abdominal pain (33.8%) and vomiting (20.3%); seven (9.5%) patients displayed gastrointestinal hemorrhage but there were no cases of intestinal intussusception.

Forty-eight patients had either arthritis or arthralgia in at least one joint (64,9%); the majority had monoarticular (39.0%) or oligoarticular (51.2%) complaints. The most affected joints were ankle/foot joints (77.1%) while others such as knee joint (22.9%) and hand/wrist joints (14.6%) were less commonly implicated.

Findings of proteinuria and hematuria were uncommon; five patients presented proteinuria, two presented hematuria and one other patient displayed both. Of the 42 boys, nine (21.4%) had either rash or edema of the scrotum. Additionally, two patients presented with bilateral palpebral edema, one of which also with bilateral conjunctivitis.

Kawasaki's disease

Forty patients were included (Table 4) and three were transferred from another hospital center and had missing data from the primary evaluation and were thus excluded. All 37 patients had fever, with a mean duration of 9.6 ±2.1 days, with six cases of fever lasting at least two weeks. The American Heart Association criteria of diagnosis for complete KD were met in 62% of patients. There was no significant difference in age at onset between those with complete and incomplete diagnosis (p=0.616). Three patients had two or less criteria present (one case without any of the main clinical features aside from fever); however, coronary artery dilation was detected, which confirmed diagnosis and prompted treatment.

Nearly all patients presented with rash (94.6%), with variable characteristics. The most common descriptions were that of a macular or maculopapular rash (19.4% and 22.6%, respectively); others also described as having a micropapular rash (22.6%). The most frequent site affected was the torso (80.0%), followed by the limbs (54.3%). Twenty-six patients developed bilateral conjunctivitis (70.3%) and 16 patients had enlarged cervical lymph nodes (43.2%).

Oropharyngeal changes were also observed in 30 patients (81.1%). Pharyngitis was the most common finding (59.5%), but other features as mucositis and cheilitis were also frequent (51.4% and 48.6%, respectively). Evidence of a strawberry tongue, a characteristic symptom of KD, was seen in 15 patients (40.5%).

Ten patients had joint involvement with either pain or inflammation (27.0%). Of these patients, five had oligoarticular complaints, three monoarticular and two polyarticular. More than half of the cases presented with peripheral edema (59.5%), 15 patients had palmar plantar erythema (40.5%) and 17 patients had desquamation in subacute phase (45.9%).

Five children had abnormalities in cardiac auscultation (tachycardia, gallop or dampening of sounds; 13.5%), one of those patients with myocarditis shown on echocardiography. Five patients had echocardiographic dilation of coronary arteries, but only one boy maintained an aneurism of the left anterior descending artery for at least five years (until the end of follow-up). The authors weren't able to identify any difference between patients that developed coronary dilation and those who did not.

Behçet's syndrome

Data concerning BS is detailed in Table 5. All patients had recurrent oral aphthous ulcers and most had genital ulcers (87%). In one patient it was also reported several episodes of epididymitis (4.3%). Only 65% of patients met the full criteria for diagnosis proposed by Koné-Paut *et al* in 2016.[13] Nevertheless, of the eight patients not meeting at least three criteria, three presented arthritis besides oral and genital ulcers, and one had esophagic ulcerations.

Skin involvement was seen in 10 patients with pseudofolliculitis (43.5%), two of which also presented with erythema nodosum (8.7%). Five had ophthalmic involvement (21.7%): panuveitis in three patients, one isolated case of conjunctivitis and another of blepharitis. Retinal vasculitis was also found in one of the patients with panuveitis.

Central nervous system involvement was less common but was still reported in four cases (17.4%). Two patients had central venous sinus thrombosis (CVST), one had seizures and the most exuberant case presented with left facial central palsy, left hemihypoesthesia, headache and ataxia.

Vascular involvement was identified in six patients (26.1%); all had venous involvement and one also suffered from a pulmonary infarction. In four patients there was evidence of upper gastrointestinal tract ulcers, one with upper gastrointestinal bleeding.

Polyarteritis nodosa

The three patients included fulfilled the mandatory criteria of either histological evidence of small or mid-size artery necrotising vasculitis or angiographic abnormalities.

Two patients were further diagnosed with DADA2, a deficiency of adenosine deaminase 2 caused by loss-of-function mutations in the ADA2 encoding gene. One is a boy with prenatal diagnosis of Klinefelter syndrome, whose parents are healthy first cousins; the other a girl who presented with symptoms at only seven months of age.

Both patients underwent genetic testing and ADA2 activity was determined. In one patient there were detected two pathogenic variants in ADA2 gene, c.1373 T > A (p.(Val458Asp)) and c.973-2A > G (p?), both in heterozygosity, associated to a reduced enzymatic activity of

ADA2 of 0.9 U/L (normal reference >5.15 U/L). A novel ADA2 homozygous variant, c.1226C > A p.(Pro409His) (reference sequence NM_001282225.1) was detected in the other patient, also associated to a reduced ADA2 activity (0.4 U/L).

There was no evidence of mucocutaneous symptoms at presentation in our sample. However, the two patients with DADA2 eventually presented mucocutaneous involvement: one patient developed livedo reticularis in the lower limbs and oral ulcers, the other patient presented a recurrent maculopapular rash. Only one patient presented with myalgia. Systemic hypertension was detected in the three patients and all required anti-hypertensive medication. None of the two boys included had testicular pain.

One patient presented mild proteinuria. Fever higher than 38ºC was detected in all three patients and two of them had complaints of abdominal pain.

There were CNS-associated symptoms in all patients. One patient suffered from an intracerebral hemorrhage due to CVST and received a decompressive craniectomy, other suffered from brain and spinal strokes and the last presented with left oculomotor nerve palsy and left hemiparesis.

Takayasu's arteritis

Only one patient with TA was included in our study. The girl presented with arterial hypertension and renal dysfunction at nine years of age.

On subsequent investigations, a magnetic resonance angiography detected a left renal artery stenosis higher than 75%, as well as mild thickening of abdominal aorta and left carotid artery walls.

Four years later she developed limb claudication which eventually remitted. Other symptoms reported were myalgia, intermittent fevers, headaches, and paresthesia.

In the seven years following diagnosis she underwent four angioplasty surgeries; first on both renal arteries followed by two on the aortoiliac region.

Currently, she is an asymptomatic adult and had a successful pregnancy.

Discussion

Vasculitides in children are a group of heterogenous diseases which can present with multiple and unspecific symptoms. The complexity of these diseases, due to its rarity and frequent misdiagnosis, makes it important to clearly ascertain what symptoms and signs should physicians be paying careful attention to. Each specific vasculitis assessed has different key symptoms. From the palpable purpura in IgAV, the prolonged fever in KD, to the oral and genital ulcers of BS, these symptoms typically alert physicians to a possible diagnosis. Nevertheless, there are several other complaints and signs shown by our patients, some of them overlapping between vasculitides and others very atypical, such as recurrent epididymitis in BS due to microvasculitis. We can state that most of our findings are in concordance with current literature, with some notable exceptions, mainly concerning renal involvement in IgAV, fever duration and articular manifestations in KD and ophthalmic involvement and vascular events in BS.

The age of the children enrolled in each group was, as expected, lower in KD and IgAV and higher in BS, albeit not significantly different. It is well established that BS usually arises later in life, mostly between the second and third decades. Karincaoglu *et al* selected only cases of juvenile-onset BS and the mean age at diagnosis was 12.3 years old, very similar to our findings.[15] All three patients diagnosed with PAN had less than 10 years of age, one case was only 10 months old. This diagnosis is extremely rare in Pediatrics and evidence on the subject is scarce. A recent study by Lee *et al* analyzed nine patients with PAN and observed a median age of diagnosis of 7.7 years old; the youngest patient was 3.5 years old.[16] DADA2 has a widely variable phenotype but may present as a vasculitis that meets clinical criteria for PAN.[17] DADA2 requires a different treatment approach (anti-TNF), presents a higher bleeding risk and needs lifelong treatment, highlighting the clinical importance of searching for this mutation in cases of PAN, as we performed in our patients. Female predominance was only observed in BS. Some authors pointed out that gender distribution in BS is highly variable around the world, with male to female ratios as low as 0.3:1 in the USA, and higher in countries such as Tunisia and Saudi Arabia (2.1-3.4:1).[18–20] An additional question regards the influence of age of onset on gender distribution. A study on a Turkish population observed a lower male to female ratio in pediatric vs. adult age onset (0.83:1 and 1.2:1, respectively).[15]

Gastrointestinal symptoms were common and non-specific across all subtypes of vasculitis. The proportion of children complaining with abdominal pain in the IgAV group (33.8%) was slightly lower than reported in a study from southern Sweden[21], and much lower than in a Japanese population-based study (75%)[21,22]. GI bleeding was a less frequent finding, and no patient developed an intestinal intussusception, which demonstrates how rare this complication

is.[23] An Italian study with 150 patients with IgAV mentions one single case of intestinal intussusception[23].

The prevalence of joint involvement as a presenting symptom is said to be around three quarters of patients in some studies, even though there are vast differences in findings reported in literature, from less than 50% to more than 90% in others[21–23]. IgAV was the subtype of vasculitis with higher joint involvement (64.86%), mainly ankle arthritis. Arthralgia and arthritis are rarely assessed in most studies about KD. We observed a significant number of KD patients with these complaints (27%), perhaps warranting more attention to joint involvement in this disease.

Renal involvement in IgAV was surprisingly lower than expected (<10%). Most studies report 20 to >50% of patients with renal involvement. Such difference in literature likely reflects distinct definitions of renal involvement, which can vary from mild proteinuria to proteinuria in the nephrotic range. We may have missed some data since some patients performed routine urinary analysis during follow-up outside of our hospital (in primary care facilities), which was not systematically registered in our electronic records. Despite that fact, which may have underdiagnosed cases of mild and transitory proteinuria or hematuria, we only reported three cases of long-term renal complications that required corticosteroid treatment.

We observed that about one fifth of the boys diagnosed with IgAV developed scrotal symptoms. These findings are very similar to other studies and highlight the importance of a thorough physical examination in cases of IgAV.

A persistent high fever lasting longer than five days, usually minimally responsive to antipyretic agents, is one of the chief presenting symptoms in KD. The patients enrolled in our study had a higher duration of fever than other reported studies. Two studies, one from a Chinese and another from a Canadian population observed a mean duration of 6.1 and 6.7 days, respectively, which is around three days shorter in comparison to our findings (9.62 days) [24,25]. This may be explained by an increase of diagnosis of incomplete and atypical forms of KD in recent years, which are usually diagnosed after more frequent pathologies are excluded. Despite this fact, only 14% of the children in KD's group were found to have echocardiographic abnormalities, which is similar to the percentage obtained in a Nationwide Survey in Japan in 2017-2018 in 32 236 patients (12%)[26]. Studies have reported diverging results concerning the prevalence of cervical lymphadenopathies in KD, ranging from 34% to 70%[24,25,27,28]. We observed that only less than half of our patients had cervical lymphadenopathies, but this signal is often overlooked and not registered, since it is non-specific and common after respiratory tract infections in children.

All patients with BS presented with oral aphthosis; genital ulcers were also highly prevalent in our study (87%) as well as in several published studies, despite some series reporting only one third of their patients with this symptom[29,30]. We observed a much lower ophthalmic involvement in BS (22%) compared to other studies. An international population-based study by Koné-Paut *et al* identified 60% of patients with ocular signs; other studies with smaller numbers (around 30-40%), albeit still higher than ours[29,31,32]. We did not encounter a clinical explanation for this finding, however we should emphasize that all patients were referred for a formal ophthalmologic examination, so misdiagnosis is unlikely.

On the other hand, the children enrolling in our study seemed slightly more likely to have any kind of vascular event. This is reported to occur in around 10 to 20% of cases; however, we observed that 30% of our patients suffered from vascular complications, 90% of which were due to venous thrombosis[15,29,31,32]. As this is a serious complication, physicians need to pay careful attention, even more so in populations where these findings seem to be more common.

Treatment

Most patients with IgAV diagnosis were given symptomatic treatment only. Twenty-two patients were treated with oral prednisolone (29.7%) and four with intravenous methylprednisolone (5.4%).

Intravenous immune globulin (IVIG) was given to all patients with KD, except one. The median time from fever onset to administration was 6.5 days (IQR 6-8). Twenty-eight patients were treated with a 2 g/kg dose (84.8%). Four needed an additional dose, one of which still had persistent fever after the second dose.

Aspirin was given to all patients. The doses used varied between 30-90 mg/kg/day. Some patients needed corticosteroid therapy and were given oral prednisolone (24.3%), some of which were also given intravenous methylprednisolone (16.2%).

Most patients with BS diagnosis were treated with colchicine (91.3%). Oral prednisolone was used in thirteen patients (56.5%) and no patient needed intravenous corticosteroids. Five patients were anticoagulated due to venous thrombosis (21.7%).

Other drugs were used in some patients such as methotrexate and azathioprine, albeit less frequently (21.7% and 17.4%, respectively). Three patients required biological therapy; two were treated with infliximab and the latter with adalimumab.

Patients with PAN diagnosis were treated with corticosteroids and induction therapy with cyclophosphamide for 6 months, followed by maintenance treatment with azathioprine, aspirin, and angiotensin-converting enzyme inhibitor.

Both patients further diagnosed with DADA2 were switched to adalimumab and showed clinical and laboratory improvement.

The single patient with TA was treated with azathioprine and anticoagulation therapy. She also underwent several angioplasties.

Limitations showed be pointed out to our study, mainly due to its retrospective nature. Four percent of patients were excluded due to missing data.

Conclusions

In summary, we concluded that clinical symptoms presented were mostly in the same range as other studies previously published, with some particularities which we have discussed. To validate our results, other pediatric studies in Portugal are warranted. The authors further suggest that multicentric international population-base studies would increase the knowledge of pediatric primary vasculitides. It would also provide much needed networks to facilitate ongoing research and clinical trials in this area, as suggested by the SHARE initiative.

Tables and Figures

	Classification criteria	Symptoms assessed	
IgA Vasculitis	EULAR/PrES 2008[14]	Purpura Abdominal pain GI Hemorrhage Intestinal intussusception Other GI symptoms Arthritis or Arthralgia Affected joints	Proteinuria Hematuria Arterial hypertension Scrotal involvement CNS Involvement Ophthalmic involvement Pulmonary involvement
Kawasaki's Disease	American Heart Association 2017[11]	Fever (and duration) Bilateral conjunctivitis Cervical lymphadenopathy Exanthema (and type) Mucositis Cheilitis Lips' erythema Strawberry tongue Pharyngitis Peripheral edema Palmar plantar erythema Skin peeling Beau lines Arthritis or Arthralgia	Tachycardia Cardiac gallop Cardiac sound dampening Coronary arteries dilation on echography Hepatomegaly Diarrhea Vomiting Abdominal pain Feeding refusal Irritability Coughing Rhinorrhea
Behçet's Syndrome	Koné-Paut I., et al. 2016[13]	Oral ulceration Genital ulceration Other GU changes Arthritis Pseudofolliculitis Erythema nodosum Ophthalmic involvement	CNS Involvement Venous vascular disease Arterial vascular disease Pulmonary involvement Renal involvement GI involvement Cardiac involvement
Polyarteritis Nodosa	EULAR/PrES 2008[14]	Livedo Cutaneous nodules Cutaneous infarction Arthralgia Myalgia Arterial hypertension Peripheral neuropathy	Proteinuria Hematuria Fever Testicular pain Abdominal pain CNS Involvement
Takayasu's Arteritis	EULAR/PrES 2008[14]	Peripheral pulse changes Exercise induced claudication and/or angina Tactile fremitus or murmur above the aorta or main branches Difference >10mmHg in SBP between 2 limbs Arterial hypertension	Elevation of acute phase reactants Constitutional symptoms Arthralgia/Myalgia Cutaneous lesions Neurological symptoms Respiratory symptoms GI symptoms Parotitis

Table I - **Classification criteria considered and specific symptoms assessed for each vasculitis**

EULAR/PReS: European Alliance of Associations for Rheumatology/Paediatric Rheumatology European Society; GI: Gastrointestinal; CNS: Central Nervous System; GU: Genitourinary

Table II. Demographic data in the different study groups

	Patients (N)	Age at diagnosis (years)*	Gender		Ethnicity	Nationality			
			Male	Female	Caucasian	Hispanic	Eastern european	Portuguese	Other
IgA Vasculitis	74	6.02 (4.48-8.16)	42	32	73	0	1	72	2
Kawasaki's disease	37	2.26 (1.07-6.20)	24	13	36	1	0	36	1
Behçet's syndrome	23	13.41 (10.19-16.75)	9	14	23	0	0	23	0
Polyarteritis nodosa	3	10(mo), 6, 8	2	1	3	0	0	3	0
Takayasu's arteritis	1	9	0	1	1	0	0	1	0
Total	138	6.05 (3.40-9.02)	77	61	136	1	1	135	3

** Age is expressed in median (IQR)*

Mo: months old

Table III. Symptoms assessed in the patients diagnosed with IgA Vasculitis

	IgA Vasculitis (N=74)
Purpura, n (%)	74 (100)
Abdominal pain, n (%)	25 (33.78)
GI Hemorrhage, n (%)	7 (9.46)
Intestinal intussusception, n (%)	0 (0)
Other GI symptoms, n (%)	17 (22.97)
Vomiting	15 (88.24)
Diarrhea	3 (17.65)
Hematemesis	3 (17.65)
Hematochezia	1 (5.88)
Arthritis or Arthralgia, n (%)	48 (64.86)
Ankles/Feet	37 (77.08)
Knees	11 (22.92)
Hands and wrists	7 (14.58)
Elbows	2 (4.17)
Proteinuria, n (%)	6 (8.22)
Hematuria, n (%)	3 (4.11)
Arterial hypertension, n (%)	2 (2.70)
Scrotal involvement[a] , n (%)	9 (21.43)
CNS Involvement, n (%)	0 (0)
Ophthalmic involvement, n (%)	2 (2.70)
Pulmonary involvement, n (%)	0 (0)

[a] Only assessed in males GI: Gastrointestinal

Table IV. Symptoms assessed in the patients diagnosed with Kawasaki's disease

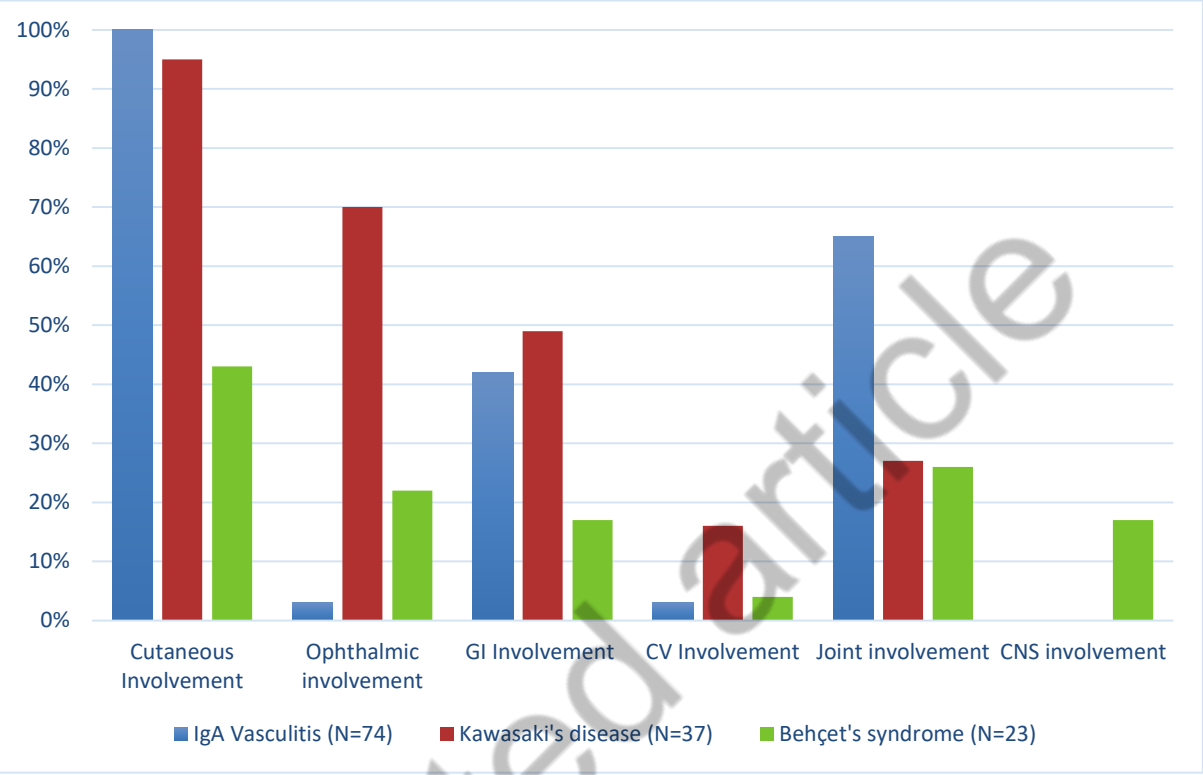
	Kawasaki's disease (N=37)
Fever, n (%)	37 (100)
duration (days), mean (±SD)	9.62 ± 6.55
Bilateral conjunctivitis, n (%)	26 (70.27)
Cervical lymphadenopathy, n (%)	16 (43.24)
Exanthema, n (%)	35 (94.59)
Mucositis, n (%)	19 (51.35)
Cheilitis, n (%)	18 (48.65)
Lips' erythema, n (%)	15 (40.54)
Strawberry tongue, n (%)	15 (40.54)
Pharyngitis, n (%)	22 (59.46)
Peripheral edema, n (%)	22 (59.46)
Palmar plantar erythema (%)	15 (40.54)
Skin peeling, n (%)	17 (45.95)
Beau lines, n (%)	0 (0)
Arthritis or Arthralgia, n (%)	10 (27.03)
monoarticular	3 (30.00)
oligoarticular	5 (50.00)
polyarticular	2 (20.00)
Tachycardia, n (%)	4 (10.81)
Cardiac gallop, n (%)	2 (5.41)
Cardiac sound dampening, n (%)	1 (2.70)
Coronary arteries dilation on echography, n (%)	5 (13.51)
Hepatomegaly, n (%)	6 (16.22)
Diarrhea, n (%)	4 (10.81)
Vomiting, n (%)	11 (29.73)
Abdominal pain, n (%)	7 (18.92)
Feeding refusal, n (%)	16 (43.24)
Irritability, n (%)	6 (16.22)
Coughing, n (%)	13 (35.14)
Rhinorrhea, n (%)	11 (29.73)

Table V - Symptoms assessed in the patients diagnosed with Behçet's syndrome

	Behçet's syndrome (N=23)
Oral ulceration, n (%)	23 (100)
Genital ulceration, n (%)	20 (86.96)
Other GU changes [a], n (%)	1 (4.35)
Arthritis, n (%)	6 (26.09)
Pseudofolliculitis, n (%)	10 (43.48)
Erythema nodosum, n (%)	2 (8.70)
Ophthalmic involvement, n (%)	5 (21.74)
CNS Involvement, n (%)	4 (17.39)
Venous vascular disease, n (%)	6 (26.09)
Arterial vascular disease, n (%)	1 (4.35)
Pulmonary involvement, n (%)	1 (4.35)
Renal involvement, n (%)	0 (0)
GI involvement, n (%)	4 (17.39)
Cardiac involvement, n (%)	1 (4.35)

[a] One case of epididymitis GU: Genitourinary CNS: Central nervous system GI: Gastrointestinal

Figure 1. Comparison of symptoms reported in IgA Vasculitis (left), Kawasaki's disease (center) and Behçet's syndrome (right) groups; GI: Gastrointestinal CV: Cardiovascular CNS: Central nervous system



Supplementary material

Table S1 Pairwise comparisons of age at onset between IgAV, KD and BS groups

Pairwise Comparisons of Groups

Sample 1-Sample 2	Test Statistic	Std. Error	Std. Test Statistic	Sig.	Adj. Sig.[a]
KD-IgAV	29,588	7,643	3,871	,000	,000
KD-BS	74,279	10,535	7,050	,000	,000
IgAV-BS	44,691	9,567	4,672	,000	,000

Each row tests the null hypothesis that the Sample 1 and Sample 2 distributions are the same.

Asymptotic significances (2-sided tests) are displayed. The significance level is ,05.

[a] Significance values have been adjusted by the Bonferroni correction for multiple tests.

Table S2 Gender distribution between IgAV and KD groups

Chi-Square Test

		Groups		
		IgAV	KD	Total
Gender	Female	32	13	45
	Male	42	24	66
Total		74	37	111

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	.673[a]	1	.412
Continuity Correction	.378	1	.538
Likelihood Ratio	.679	1	.410
N of Valid Cases	111		

[a] 0 cells (.0%) have expected count less than 5. The minimum expected count is 15.00.

Table S3 Gender distribution between BS and IgAV groups

Chi-Square Test

		Groups		
		BS	IgAV	Total
Gender	Female	14	32	46
	Male	9	42	51
Total		23	74	97

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	2.186[a]	1	.139
Continuity Correction	1.537	1	.215
Likelihood Ratio	2.193	1	.139
N of Valid Cases	97		

[a] 0 cells (.0%) have expected count less than 5. The minimum expected count is 10.91

Table S4 Gender distribution between BS and KD groups

Chi-Square Test

		Groups		
		BS	KD	Total
Gender	Female	14	13	27
	Male	9	24	33
Total		23	37	60

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	3.795[a]	1	.051
Continuity Correction	2.827	1	.093
Likelihood Ratio	3.815	1	.051
N of Valid Cases	60		

[a] 0 cells (.0%) have expected count less than 5. The minimum expected count is 10.35

Table S5 Difference in age at onset between complete and incomplete KD diagnosis

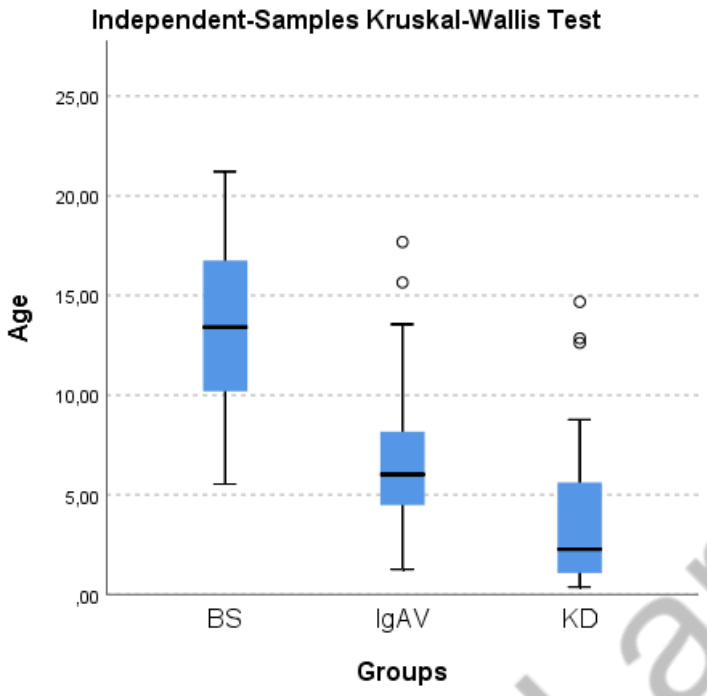
Mann-Whitney Test

	Groups	N	Mean Rank	Sum of Ranks
Age	Complete	23	19.70	453.00
	Incomplete	14	17.86	250.00
	Total	37		

	Age
Mann-Whitney U	145.000
Wilcoxon W	250.000
Z	-.501
Asymp. Sig. (2-tailed)	.616
Exact Sig. [2*(1-tailed Sig.)]	.632[a]

[a] Not corrected for ties

Fig. S1 Difference in age at onset between BS, IgAV and KD groups



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