The Egyptian Rheumatologist xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

The Egyptian Rheumatologist

journal homepage: www.elsevier.com/locate/erhe

Original Article

The distribution and outcome of vasculitic syndromes among Egyptians: A multi-centre study including 630 patients

Amira A. Shahin[a,*], Hania S. Zayed[a], Rasha M. Elrefai[a], Heba Taher[b], Ahmed Elsaie[b], Soha H. Senara[c], Hanan M. Fathi[c], Gihan Omar[d], Mervat I. Abd Elazeem[e]

[a] Rheumatology and Rehabilitaion Department, Faculty of Medicine, Cairo University, Cairo, Egypt
[b] Abu El-Reesh Pediatric Hospital, Faculty of Medicine, Cairo University, Cairo, Egypt
[c] Rheumatology and Rehabilitation Department, Faculty of Medicine, Fayoum University, Egypt
[d] Rheumatology and Rehabilitation Department, Faculty of Medicine, Minia University, Minia, Egypt
[e] Rheumatology and Rehabilitation Department, Faculty of Medicine, Bani-Suef University, Bani-Suef, Egypt

ARTICLE INFO

Keywords:
Vasculitis damage index
Vasculitis
Behçet's disease
HCV-associated vasculitis
Egypt

ABSTRACT

Aim of the work.: Studies describing the epidemiology of vasculitis in the Middle East and Africa are limited. The aim of this multi-centre study is to describe the distribution and outcome of vasculitic syndromes among Egyptian vasculitis patients seen by rheumatologists.

Patients and Methods: The files of patients diagnosed with vasculitis between January 2002 and December 2016 were reviewed and were classified according to The Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis CHCC 2012 and disease- specific criteria. The vasculitis damage index (VDI) was calculated for all patients at the last visit.

Results: Six hundred and thirty patients with ages ranging from of 9 months-74 years, including 264 (41.9%) males and 366 (58.1%) females were studied. Vasculitis associated with hepatitis C virus (HCV) infection was detected in 151 (24%), Behçet's disease in 148 (23.5%), Immunoglobulin A vasculitis in 101 (16%), vasculitis associated with systemic lupus erythematosus in 93 (14.8%), Takayasu's arteritis in 33 (5.2%), Kawasaki's disease in 22 (3.5%) patients, respectively. Other vasculitic syndromes were uncommon and each accounted for less than 2% of the studied cases. The VDI ranged from 0 to 13. Only 109/630 (17.3%) patients had no vasculitis-related damage (VDI = 0). Mortality was recorded in 36 (5.7%) patients; out of these, 27 deaths were vasculitis-related.

Conclusion: HCV-associated vasculitis and Behçet's disease were the most frequently diagnosed vasculitic syndromes.

1. Introduction

The vasculitides are a heterogeneous group of uncommon diseases characterized by inflammation and necrosis of the blood vessels including arteries and veins of different sizes. Vasculitic syndromes often have overlapping clinical and pathologic manifestations making a precise diagnosis sometimes difficult [1]. The Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis CHCC1994 included categories for large-, medium- and small-sized vessel vasculitis. The latter includes the categories of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis and immune-complex mediated vasculitis [2]. The CHCC2012 added important categories that were not included in CHCC1994 nomenclature of vasculitis and constructed a specific definition for each. The CHCC2012 nomenclature includes the categories of large-, medium-, small- and variable -sized vessel vasculitis, single organ vasculitis, vasculitis associated with systemic disease and vasculitis associated with a probable etiology [3]. There are differences in the geographic clustering of vasculitides around the world which may be due to genetic or environmental factors or ascertainment. Moreover, within the same disease category, the clinical expression may vary among different populations [4]. Studies describing the epidemiology of vasculitis in the Middle East and Africa are limited [5–8]. The aim of this study is to describe the distribution and outcome of the different forms of vasculitis and the clinical manifestations of the most common vasculitic syndromes seen at five rheumatology centres from Egypt.

Peer review under responsibility of Egyptian Society of Rheumatic Diseases.
* Corresponding author.
E-mail address: amira.shahin@kasralainy.edu.eg (A.A. Shahin).

https://doi.org/10.1016/j.ejr.2018.01.001
Received 4 January 2018; Accepted 11 January 2018

2. Patients and methods

This is a multi-centre retrospective study including patients diagnosed with systemic vasculitis seen at the Rheumatology Departments of Cairo University (Kasr Alainy hospital and Abu El-Reesh Paediatric Hospital), Fayoum University, Beni-Suef University and Minia University diagnosed between January 2002 and December 2016. The region of Lower Egypt and Cairo was considered to extend from latitude 31° 12′ N, at the north of Egypt to Cairo at 30° 2′ N and Upper Egypt was considered from Cairo to Aswan which is located at 24° 8′ N. Cairo University hospitals are the largest referral centres in Egypt and receive patients from all over the country. The other three centres are located in Upper Egypt. The study complies with the Declaration of Helsinki. The locally appointed ethics committee has approved the research protocol

Patients were classified according to the CHCC2012 nomenclature of systemic vasculitis [3] and according to disease- specific criteria. The American College of Rheumatology (ACR) 1990 Criteria for the classification of giant cell arteritis [9], Takayasu arteritis [10], polyarteritis nodosa (PAN)[11], Wegener's granulomatosis (granulomatosis with polyangiitis, GPA) [12], and Churg Strauss syndrome (eosinophilic granulomatosis with polyangiitis, EGPA), [13] and the European League against Rheumatism/Paediatric Rheumatology European Society (EULAR/PReS) classification criteria for Kawasaki disease and childhood Henoch-Schönlein purpura (Immunoglobulin A (IgA) vasculitis) were applied [14]. Behçet's disease was classified according to the International Criteria for Behçet's disease [15]. Hepatitis C virus (HCV)–related vasculitis was classified according to the validated classification criteria for cryoglobulinaemic vasculitis which are also useful for classification of patients with typical manifestations even when cryoglobulins are not detected on initial laboratory testing [16]. The diagnosis of other vasculitic syndromes was confirmed either by biopsy or vascular imaging.

The patients' files were reviewed for their residence, age at disease onset (defined as the time of onset of symptoms related to vasculitis), age at diagnosis, clinical manifestations, laboratory tests, presence of an underlying connective tissue disease, probable etiologic factor e.g. drugs, chronic HCV or hepatitis B virus (HBV) infection, imaging and biopsy results if available. Vasculitis was confirmed by biopsy in 114 patients (18.1%).The cumulative damage due to vasculitis or its treatment was assessed using the vasculitis damage index (VDI) [17]. It was obtained at the last visit. All patients received treatment according to disease-specific guidelines starting from the date of diagnosis.

Statistical analysis: The retrospective data of the patients were analyzed using the statistical program SPSS version 15. Results were expressed as mean ± standard deviation (SD), or number and percentage. Correlations were expressed by Pearson correlation coefficients. Differences were considered to be significant when p value was less than 0.05.

3. Results

Six hundred and thirty patients diagnosed with vasculitis were included. Their ages at disease onset ranged from 9 months-74 years, 264 (41.9%) were males and 366 (58.1%) females; 477 patients (75.7%) were from Lower Egypt, and 153 (24.3%) from Upper Egypt. The frequency of different vasculitic disorders, the percentage of females and the age at onset of each disease are shown in Table 1.

The VDI in all cases ranged from 0 to 13. Only 109 (17.3%) patients had no vasculitis-related damage (VDI = 0); 74 had IGA vasculitis, 21 had HCV- associated vasculitis,10 had Kawasaki's disease and 4 patients had vasculitis associated with SLE. The VDI in all types of vasculitis was not related to the disease duration, but it showed a significant correlation to the time lapse between the onset of manifestations and the date of diagnosis (diagnostic delay) in large vessel vasculitis, Behçet's disease, and in vasculitis associated with systemic diseases (Table 2).

Mortality was the outcome of 36 (5.7%) patients. The cause of mortality in 5 GPA patients was severe alveolar hemorrhage. Four patients with Behçet's disease had stroke. Three patients died from vasculitis of the central nervous system (CNS); (two patients had primary CNS vasculitis and the third patient was unclassified). In nine patients with SLE associated vasculitis the cause of death was attributed to active vasculitis with multi-organ failure and infection, while six patients with HCV associated vasculitis died from infection with progressive leucopenia not associated with vasculitis activity. In the remaining 9 patients the cause of mortality was unknown or not vasculitis-related (Table 2).

Concerning the geographic distribution of vasculitis, the frequencies of KD, IGAV and HCV associated vasculitis were higher among patients from Lower Egypt (p = 0.009, p = 0.001 and p = 0.035, respectively), while Behçet's disease and ANCA-associated vasculitis were more common among patients from Upper Egypt (p = 0.001 and p = 0.04, respectively) (Table 3).

Vasculitis associated with HCV was the commonest form of vasculitis, detected in 151 (24%) patients. Table 4 shows the general, clinical and laboratory manifestations of patients diagnosed with HCV-associated vasculitis. One hundred-four (68.9%) patients had small vessel vasculitis only. Forty-seven (31.1%) patients had medium sized vessel involvement (PAN-like) with 17 (11%) having only medium sized vessel involvement and 30 (19.9%) having additional small vessel involvement. Nerve conduction velocity studies of the patients with

Table 1
The frequency distribution of vasculitic disorders in 630 cases.

	Disease	Frequency N (%)	Females N (%)	Age at onset (years)
LVV	TAK	33 (5.2)	33 (1 0 0)	32.3 ± 1.7
	GCA	3 (0.5)	2 (66.7)	56.3 ± 6
MVV	PAN	10 (1.6)	4 (40)	38 ± 15.9
	KD	22 (3.5)	7 (31.8)	3.3 ± 1.8
SVV	MPA	1 (0.2)	1 (1 0 0)	28
	GPA	11 (1.7)	9 (81.8)	34.4 ± 11.2
	EPGA	5 (0.8)	5 (1 0 0)	33.8 ± 13.1
	IGAV	101 (16)	51(50.5)	7.8 ± 3.2
	HUV	2 (0.3)	2 (1 0 0)	8,36
VVV	BD	148 (23.5)	20 (13.5)	28.4 ± 7.6
	CS	1 (0.2)	1 (1 0 0)	37
SOV	CLA	3 (0.5)	3 (1 0 0)	38 ± 16.5
	CA	2 (0.3)	1 (50)	6,28
	PCNSV	2 (0.3)	0	60
VASD	SLE	93 (14.8)	88 (94.6)	26.1 ± 10.7
	RA	7 (1.1)	6 (85.7)	44.7 ± 11.3
	DM	4 (0.6)	3 (75)	30.3 ± 13.6
	SSc	6 (0.95)	3 (1 0 0)	31.7 ± 4.2
	MCTD	4 (0.6)	4 (1 0 0)	28.5 ± 7.1
	OS	2 (0.3)	1 (50)	23,26
	IBD	1 (0.2)	1 (1 0 0)	30
VAPE	HCVAV	151 (24)	103 (68.2)	47.7 ± 11
	HBVAV	4 (0.6)	3 (75)	34.1 ± 12.1
	DAV	3 (0.5)	2 (66.7)	26.7 ± 16.4
Unclassified		10 (1.6)	8 (80)	42 ± 11.1

LVV: Large vessel vasculitis; TAK: Takayasu arteritis; GCA: Giant cell arteritis; MVV: Medium vessel vasculitis; PAN: Polyarteritis nodosa; KD: Kawasaki disease; SVV: Small vessel vasculitis; MPA: Microscopic polyangiitis; GPA: Granulomatosis with polyangiitis; EGPA: Eosinophilic granulomatosis with polyangiitis; IGAV: IgA vasculitis; HUV: Hypocomplementemic urticarial vasculitis; VVV: Variable vessel vasculitis; BD: Behcet's disease; CS: Cogan's syndrome; SOV: Single-organ vasculitis; CLA: Cutaneous leukocytoclastic angiitis; CA: Cutaneous arteritis; PCNSV: Primary central nervous system vasculitis; VASD: vasculitis associated with systemic disease; SLE: Systemic lupus erythematosus; RA: Rheumatoid arthritis; DM: Dermatomyositis; SSc: systemic sclerosis; MCTD: Mixed connective tissue disease; OS: Overlap syndrome; IBD: Inflammatory bowel disease; VAPE: vasculitis associated with probable etiology; HCVAV: Hepatitis C virus associated vasculitis; HBVAV: Hepatitis B virus associated vasculitis; DAV: Drug associated immune complex vasculitis.

Table 2
Cumulative damage and mortality in 630 vasculitis patients.

	Disease	Disease Duration (y) mean ± S.D.	Time Lapse from onset till diagnosis (m) mean ± SD	VDI mean ± SD	Mortality
LVV	TAK	2.7 ± 4.1	6.3 ± 13.3*	3.5 ± 1.3	0
	GCA	2.3 ± 1.6	9.3 ± 12.7*	2.7 ± 2.9	0
MVV	PAN	5 ± 4.7	24.7 ± 37.7	3.8 ± 1.1	0
	KD	1.6 ± 1.6	3.9 ± 1	0.9 ± 1.1	0
SVV	MPA	5	3	5	0
	GPA	3.5 ± 2.3	16.2 ± 22	4.5 ± 2.6	5
	EPGA	3.1 ± 1.9	7.8 ± 9.3	4.2 ± 0.8	0
	IGAV	0.4 ± 0.7	2.2 ± 1.1	1.1 ± 0.6	0
	HUV	1.2 ± 1.1	6.5 ± 7.8	2.5 ± 2.1	0
VVV	BD	8 ± 6.7	9.2 ± 13.2*	3.9 ± 2	12
	CS	0.5	1	3	0
SOV	CLA	6.5 ± 0.7	0.5	2	0
	CA	2.5 ± 0.7	9 ± 4.2	3 ± 1.4	0
	PCNSV	1.2 ± 1.1	2.5 ± 0.7	1.5 ± 0.7	2
VASD	SLE	4.1 ± 4.9	9.1 ± 14.2*	3.4 ± 2.1	9
	RA	2.6 ± 3.3	6.5 ± 6.8*	3.4 ± 1.6	0
	DM	3.6 ± 4.9	6.2 ± 4	2.7 ± 1.3	1
	SSc	6.5 ± 5.6	3.3 ± 1.5	3.8 ± 1.2	0
	MCTD	8.4 ± 6.3	5 ± 2.6	4.5 ± 0.6	0
	OS	3 ± 1.4	16 ± 11.3	5 ± 1.4	0
	IBD	3	2	1	0
VAPE	HCVAV	3.6 ± 4.3	5.1 ± 4.7*	2.1 ± 1.5	6
	HBVAV	0.7 ± 0.3	6 ± 4.2	2.8 ± 0.9	0
	DAV	3.5 ± 1.8	5.3 ± 4	2.7 ± 2.1	0
Unclassified		2.4 ± 3.5	8.9 ± 4.6*	4.4 ± 1.6	1

VDI: Vasculitis Damage Index; LVV: Large vessel vasculitis; TAK: Takayasu arteritis; GCA: Giant cell arteritis; MVV: Medium vessel vasculitis; PAN: Polyarteritisnodosa; KD: Kawasaki disease; SVV: Small vessel vasculitis; AAV: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; MPA: Microscopic polyangiitis; GPA: Granulomatosis with polyangiitis; EGPA: Eosinophilic granulomatosis with polyangiitis; ICV: Immune complex; CV: Cryoglobulinemic vasculitis; IGAV: IgA vasculitis; HUV: Hypocomplementemic urticarial vasculitis; VVV: Variable vessel vasculitis; BD: Behcet's disease; CS: Cogan's syndrome; SOV: Single-organ vasculitis; CLA: Cutaneous leukocytoclastic angiitis; CA: Cutaneous arteritis; PCNSV: Primary central nervous system vasculitis; VASD: vasculitis associated with systemic disease; SLE: Systemic lupus erythematosus; RA: Rheumatoid arthritis; DM: Dermatomyositis; SSc: systemic sclerosis; MCTD: Mixed connective tissue disease; OS: Overlap syndrome; IBD: Inflammatory bowel disease; VAPE: vasculitis associated with probable etiology; HCVAV: Hepatitis C virus associate vasculitis; HBVAV: Hepatitis B virus associated vasculitis; DAV: Drug associated immune complex vasculitis;*: significant correlation with the VDI.

Table 3
Distribution of vasculitic syndromes among patients from Upper and Lower Egypt.

	Upper Egypt (n = 153)	Lower Egypt (n = 477)	P value
TAK	5 (3.3)	28 (5.9)	0.223
KD	0	22 (4.6)	0.009*
AAV	8 (5.2)	9 (1.9)	0.04*
IGAV	9 (5.9)	92 (19.3)	0.001*
BD	57 (37.3)	91 (19.1)	0.001*
VASD	33 (21.6)	84 (17.6)	0.283
HCVAV	27 (17.7)	124 (26)	0.035*

TAK: Takayasu arteritis; KD: Kawasaki disease; AAV: AAV: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; IGAV: IgA vasculitis; BD: Behcet's disease; VASD: vasculitis associated with systemic disease; HCVAV: Hepatitis C virus associated vasculitis; * $p \leq 0.05$.

peripheral neuropathy revealed that 27 patients had axonal-demyelinating lesions, 34 had axonal lesion, and 14 had demyelinating lesions. While NCV studies of patients with mononeuritis multiplex revealed that 10 patients had axonal-demyelinating lesions, 3 had axonal lesion, and 5 had demyelinating lesions.

CNS involvement occurred in 6 patients in the form of personality changes, memory disturbance and depression. Magnetic resonance imaging (MRI) showed ischaemic foci of the frontal lobes in four patients and in the parietal and occipital lobes in one patient. Nephritis with urinary sediment was detected in 26 (17.2%) patients; 14 patients had renal biopsy which showed membrano proliferative glomerulonephritis.

Liver biopsy or Fibroscan results were available for 83 patients (29 patients had a liver biopsy and 54 had a Fibroscan). Ten patients (12%) had chronic active hepatitis by biopsy, while 23 (27.7%) of the patients had severe liver fibrosis or cirrhosis (14 patients were diagnosed by biopsy, and 9 by Fibroscan: F3 & F4).

Behçet's disease was the second most common type of vasculitis. It

Table 4
General, clinical and laboratory manifestations of 151 patients with HCV-associated vasculitis.

Clinical Manifestations	Number	%
Age at diagnosis (years) mean ± SD	44.4 ± 11.1	
Male: Female	48:103	
Duration of symptoms (years) mean ± SD	3.7 ± 4.6	
Cutaneous involvement	131	86.1
Digital gangrene	24	15.9
Cutaneous ulcer	24	15.9
Purpura	94	62.3
Musculoskeletal involvement	76	50.3
Arthritis	48	31.8
Arthralgia	28	18.5
Neurological involvement	93	61.6
Peripheral neuropathy	75	49.7
Mononeuritis multiplex	18	11.9
Central nervous system involvement	6	4.5
Weakness	23	15.2
Interstitial pulmonary fibrosis	11	7.3
Nephritis	26	17.2
Rheumatoid factor	64	42.4
Antinuclear antibodies	20	13.2
Cryoglobulins	52	34.4
Consumed C3	52	34.4
Consumed C4	66	43.7

Table 5
General and clinical manifestations of 148 patients diagnosed with Behcet's Disease.

Clinical Manifestations	Number	%
Age at diagnosis (years) mean ± SD	28.4 ± 7.6	
Male: Female (number)	128:20	
Duration of symptoms (years) mean ± SD	8.2 ± 6.7	
Oral ulcers	148	100
Genital ulcers	140	94.6
Cutaneous involvement	60	40.5
Erythema nodosum	34	23
Macules, nodules, ulcers, purpura	44	29.7
Digital gangrene	5	3.4
Articular involvement	69	46.6
Arthritis	34	23
Arthralgia	35	23.6
Pulmonary infarction	3	2
Neurological Involvement	40	27
Peripheral neuropathy	20	13.5
Sensory neuropathy	15	10.1
Motor neuropathy	3	2
Sensory-motor neuropathy	2	1.4
CNS	25	16.9
Stroke	13	8.8
Cognitive disorder	10	6.8
Major psychosis	7	4.7
Cranial nerve involvement	7	4.7
Seizures	1	0.7
MRI vasculitis	19	12.8
Ocular Involvement	86	58.1
Retinal involvement	44	29.7
Retinal vasculitis	23	15.5
Optic neuritis	2	1.4
Retinal vein occlusion	4	2.7
Retinal artery occlusion	3	2
Retinitis	12	8.1
Uveitis	78	52.7
Anterior	31	20.9
Posterior	21	14.2
Panuveitis	26	17.6
Vascular Occlusion	37	25
Extremities	34	23
Aorta	1	0.7
Pulmonary	1	0.7
IVC, SVC, Budd Chiari	5	3.4
Myocardial infarction	3	2

CNS; central nervous system, IVC; inferior vena cava, SCV; superior vena cava.

was diagnosed in 148 patients (23.5%). The male to female ratio among BD patients was 6.4. The general and clinical manifestations of BD patients are shown in Table 5.

Finally, we had 10 (1.6%) vasculitis cases that could not be classified into any category. None of these patients was positive for antiphospholipid antibodies. Their clinical manifestations are shown in Table 6.

4. Discussion

This is the first multi-centre study describing the distribution of vasculitides in Egypt. Vasculitis related to HCV infection and Behçet's disease were the most frequently diagnosed types of vasculitis accounting for 24% and 23.5% of the studied cases, respectively. Furthermore, there were significant differences in the distribution of vasculitic syndromes between Lower and Upper Egypt. Kawasaki's disease was only reported in Lower Egypt, IgA vasculitis and HCV-associated vasculitis were more common in Lower Egypt while ANCA-associated vasculitis and Behçet's disease were more frequently diagnosed in Upper Egypt.

Egypt has the highest prevalence of HCV infection worldwide. According to the most recent national Egyptian health issue survey in 2015, in the 15–59-year age groups, the overall prevalence of HCV antibody was found to be 10.0% and that of HCV RNA to be 7.0%. The prevalence of HCV infection in Lower Egypt (HCV antibodies 12.2%, HCV RNA 8.7%) was higher than in Upper Egypt (HCV antibodies 8.7%, HCV RNA 5.8%) [18]. In the present study, HCV-related vasculitis was more frequently diagnosed among patients from Lower Egypt and Cairo which could be attributed to the higher prevalence of HCV infection in Lower Egypt. With the current government sponsored mass treatment program using the direct acting antiviral drugs which can lead to viral eradication in up to 98% of infected patients, these figures are expected to decline [19]. Chronic HCV infection may be considered a systemic disease that can induce various extrahepatic manifestations in up to two thirds of infected individuals. Many of these are autoimmune in nature with cryoglobulinaemic vasculitis being the most distinctive manifestation [20]. HCV cryoglobulinaemic vasculitis is classified as a small vessel leucocytoclastic vasculitis that can affect small and medium sized blood vessels [21], less commonly, a medium sized PAN –like vasculitis may occur in the setting of HCV infection, accounting for 19.3% of 161 patients in one series [22]. In the present study, 31.1% of HCV-related vasculitis presented with PAN-like manifestations. HCV vasculitis may occur in the absence of detectable cryoglobulins, accounting for 11% of 151 cases [23]. Cryoglobulins may not be detected in HCV vasculitis patients with typical clinical manifestations due to low circulating immunoglobulin levels especially early in the disease, tissue deposition of immune complexes and methodological issues [16]. In the present study, only 34.4% of HCV-related vasculitis patients had detectable cryoglobulins in serum. The most frequent manifestations of HCV-related vasculitis were purpura (65–86%), weakness (70–97%), arthralgia (31–92%), peripheral neuropathy (50%-79%)and renal involvement (15–33%) in studies from France, Italy and Spain [23–25]. Severe liver fibrosis (F3-F4) or cirrhosis have been found in 33–44% of HCV vasculitis patients [23,25]. The manifestations of HCV vasculitis in the present study are comparable to previous studies [23–25], but the frequencies of fatigue and severe liver fibrosis were lower (15.2%and

Table 6
The unclassified cases of systemic vasculitis.

	Age (years)	Gender	Clinical manifestations	Investigations	Biopsy
Case 1	22	Female	Mononeuritis multiplex, arthralgia	Occluded peripheral vessel, consumed C4, Axono-demyelinating neuropathy on NCVs	–
Case 2	21	Female	Digital gangrene, arthralgia	Occluded peripheral vessel, Consumed C3, C4	–
Case 3	46	Female	Digital gangrene, retinal vasculitis, major psychosis, DVT, PN	Attenuated, occluded peripheral vessel, Axonal neuropathy by NCVs, Fluorescein angiography	–
Case 4	30	Female	Arthritis, digital gangrene	Attenuated thickened peripheral vessels	–
Case 5	60	Female	Arthritis, digital gangrene, Raynaud's, PN	Axonal neuropathy by NCVs, consumed C3	+
Case 6	42	Female	Digital gangrene, PN, stroke, DVT	CNS vasculitis in MRI, Axono-demyelinating neuropathy by NCVs	–
Case 7	42	Male	Digital gangrene, skin ulcer, retinal vasculitis	Fluorescein angiography	+
Case 8	43	Female	Skin Ulcer, PN, stroke	CNS vasculitis in MRI, Axono-demyelinating neuropathy by NCVs	+
Case 9	50	Female	Digital gangrene, skin ulcer, retinal vasculitis	Fluorescein angiography	+
Case 10	62	Male	Arthritis, retinal vasculitis, diplopia, stroke	CNS vasculitis in MRI, Fluorescein angiography	–

C3; complement 3, CNS; central nervous system, DVT; deep venous thrombosis, MRI; magnetic resonance imaging, NCVs; nerve conduction velocity study, PN; peripheral neuropathy, (+); vasculitis diagnosed by biopsy, (-); biopsy not done.

27.7%, respectively).

Behçet's disease is most prevalent along the ancient Silk Road and it is more common in the Far East and Middle East. The highest prevalence is seen in Turkey, followed by Iran [26]. Behçet's disease in the present study accounted for 23.5% of the studied patients while it represented 63.3% of 721 vasculitis patients from North Eastern Iran [27] and 13.6% of 1064 vasculitis patients from India [28]. Notably, both studies only included primary vasculitic syndromes (thus excluding the categories of vasculitis associated with a systemic disease and vasculitis associated with probable etiology). Egyptian studies describing the clinical manifestations in Behçet's disease were performed in individual centres and included a smaller number of patients and thus show several discrepancies compared to the present study [29,30]. In the present study, Behçet's disease was more common in males (male: female ratio = 6.4). The male: female ratio was 1.7 [30], and 30.5 [29] in two Egyptian studies, while a larger study [31] showed a male: female ratio of 5.7 which is comparable to the results of this study. In two Iranian studies, the male: female ratio was nearly equal [26,27]. The mean age at disease onset was 28.4 ± 7.6 years which is comparable to other studies [26,27,32]. Similar to the study by Davatchi et al. (on 6500 patients) [26], mucocutaneous, ocular and articular manifestations were the most common manifestations. Cutaneous manifestations affected 40.5% of the studied patients, while they affected 10.5% [30] and 55.5% [29] of patients in other Egyptian studies and 64.9% of Iranian patients [26]. Ocular inflammation affected 58.1% of the patients which is comparable to others [26,29] but less than the frequency in another Egyptian study (73.7%) [30]. In the present study, neurological involvement was in 27% which is comparable to another Egyptian study [30], but less frequent than others (34.9%) [29], and higher than in the Iranian study (3.8%). Vascular involvement was seen in 25% of the patients while it was not found in any [30] and in 57.1% [29] in other Egyptian studies and in 8.3% in Iranians [26]. None of our patients had gastrointestinal involvement versus 10.5% [30] and 19% [29] in other Egyptian studies and 7.4% in Iranians [26].

Takayasu arteritis and giant cell arteritis are classified as large vessel vasculitis and are histologically similar. While Takayasu arteritis is more common than giant cell arteritis in Japan, the opposite is true for European and North American countries [33]. In our study, the frequency of Takayasu arteritis was 5.2% while that of giant cell arteritis only 0.5%. Also in India, Takayasu arteritis was more common than giant cell arteritis (20.2 vs 3.4%, respectively), [28] while in Iran, the frequencies were closer (6.3 vs 4% for Takayasu arteritis and giant cell arteritis, respectively [27]. Kawasaki's disease is most common in the Far East especially Japan, Korea and China and relatively uncommon in USA and Europe [4]. In the present study, Kawasaki's disease accounted for 3.6% of the studied cases. IgA vasculitis was diagnosed in 16% which is more frequent than a study from Iran (3.5%) [27] but less frequent than the study from India [28].

ANCA associated vasculitic syndromes are more common in Caucasian populations than non– Caucasians and they are relatively uncommon among African Americans [34]; in a study from New Zealand, GPA was found to be twice as common in Europeans than Maoris or Asians [35]. ANCA associated vasculitic syndromes in the present study were uncommon, accounting together for 3.4% of the studied cases. PAN was diagnosed in 2% of the patients while other forms of vasculitis were less frequent. Finally, we had 10 (1.6%) cases that could not be classified into any category implying the need to develop new diagnostic and classification criteria for vasculitis.

Damage in systemic vasculitis represents the chronic scarring due to vasculitis which has accumulated during the course of the disease and may be due to the vasculitis itself, its treatment or comorbidities. The VDI is a validated tool which is used to assess morbidity in systemic vasculitis and may serve as an outcome measure in clinical trials [17,36]. In the present study, the VDI was used to represent the cumulative irreversible organ damage of the patients at their last visit. The majority of the studied patients (82.7%) had some form of vasculitis-related damage. The VDI was not found to be related to the duration of symptoms in any of the vasculitic syndromes, however, it was significantly correlated with the time lapse between the onset of disease manifestations and the date of diagnosis in Takayasu arteritis, giant cell arteritis, Behçet's disease, vasculitis secondary to SLE and RA and HCV associated vasculitis. This emphasizes the necessity to diagnose vasculitis early to start specific treatment and improve the disease outcome. Finally, 36 (5.7%) of the patients had a fatal outcome, mainly due to active disease and/or infection.

To conclude, HCV-related vasculitis infection and Behçet's disease were the most frequently diagnosed types of vasculitis. Moreover, significant differences have been shown regarding the distribution of vasculitic syndromes between Lower and Upper Egypt. While this study describes the frequency of different types of vasculitis seen by adult and paediatric rheumatologists, it cannot be considered an epidemiologic profile. Patients with vasculitis may present to different medical specialties according to their initial manifestations. Further epidemiologic studies involving different medical specialties are needed to establish the incidence and prevalence of these heterogeneous disorders in Egypt.

Conflict of interest

We have no conflict of interest to declare.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] González-Gay MA, García-Porrúa C. Epidemiology of the vasculitides. Rheum Dis Clin North Am 2001;27:729–49.
[2] Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum 1994;37:187–92.
[3] Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013;65:1–11.
[4] Watts RA. Epidemiology of vasculitis – lessons learnt from the differences in different geographical areas. Indian J Rheum 2015;10:S6–10.
[5] Chaudhry IA, Shamsi FA, Elzaridi E, Arat YO, Bosley TM, Riley FC. Epidemiology of giant-cell arteritis in an Arab population: a 22-year study. Br J Ophthalmol 2007;91:715–718.
[6] Hatemi G, Seyahi E, Fresko I, Talarico R, Hamuryudan V. Behçet's syndrome: a critical digest of the 2014–2015 literature. Clin Exp Rheumatol 2015;33:S3–14.
[7] Boudiaf H, Achir M. The clinical profile of Kawasaki disease in algerian children: a single institution experience. J Trop Pediatr 2016;62:139–43.
[8] Khalifa M, Karmani M, Jaafoura NG, Kaabia N, Letaief AO, Bahri F. Study Group of GCA in Tunisia. Epidemiological and clinical features of giant cell arteritis in Tunisia. Eur J Intern Med 2009;20:208–12.
[9] Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33:1122–8.
[10] Arend WP, Michel BA, Bloch DA, Hunder GG, Calabrese LH, Edworthy SM, et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum 1990;33:1129–34.
[11] Lightfoot RW, Michel BA, Bloch DA, Hunder GG, Zvaifler DJ, Mc Shane DJ, et al. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. Arthritis Rheum 1990;33:1088–94.
[12] Leavitt RY, Fauci AS, Bloch DA, Michel BA, Hunder GG, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum 1990;33:1101–7.
[13] Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 1990;33:1094–100.
[14] Ozen S, Ruperto N, Dillon MJ, Bagga A, Barron K, Davin JC, et al. EULAR/PReS endorsed consensus criteria for the classification of childhood vasculitides. Ann Rheum Dis 2006;65:936–41.
[15] Davatchi F, Assaad-Khalil S, Calamia KT, Crook JE, Sadeghi-Abdollahi B, Schirmer M, et al. The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. J Eur Acad Dermatol Venereol 2014;28:338–47.
[16] Quartuccio L, Isola M, Corazza L, Ramos-Casals M, Retamozo S, Ragab GM, et al. Validation of the classification criteria for cryoglobulinaemic vasculitis. Rheumatology (Oxford) 2014;53:2209–2213.

[17] Exley AR, Bacon PA, Luqmani RA, Kitas GD, Gordon C, Savage CO, et al. Development and initial validation of the Vasculitis Damage Index for the standardized clinical assessment of damage in the systemic vasculitides. Arthritis Rheum 1997;40:371–80.
[18] Kandeel A, Genedy M, El-Refai S, Funk AL, Fontanet A, Talaat M. The prevalence of hepatitis C virus infection in Egypt 2015: implications for future policy on prevention and treatment. Liver Int 2017;37:45–53.
[19] El-Fishawy H, Saadi G, Hassaballa M, Hussein M, Doss W, Ragab G, et al. Antiviral treatment prioritization in HCV-infected patients with extrahepatic manifestations - an Egyptian perspective. J Adv Res 2016;7:391–402.
[20] Cacoub P, Poynard T, Ghillani P, Charlotte F, Olivi M, Piette JC, et al. Extrahepatic manifestations of chronic hepatitis C. MULTIVIRC Group. Multide partment Virus C. Arthritis Rheum 1999;42:2204–12.
[21] Ferri C. Mixed cryoglobulinemia. Orphanet J Rare Dis 2008;3:25.
[22] Saadoun D, Terrier B, Semoun O, Sene D, Maisonobe T, et al. Hepatitis C virus-associated polyarteritis nodosa. Arthritis Care Res (Hoboken) 2011;63:427–35.
[23] Terrier B, Semoun O, Saadoun D, Sène D, Resche-Rigon M, Cacoub P. Prognostic factors in patients with hepatitis C virus infection and systemic vasculitis. Arthritis Rheum 2011;63:1748–57.
[24] Antonelli A, Fallahi P, Ferrari SM, Frascerra S, Mancusi C, Colaci M, et al. High circulating chemokines (C-X-C motif) ligand 9, and (C-X-C motif) ligand 11, in hepatitis C-associated cryoglobulinemia. Int J Immunopathol Pharmacol 2013;l26:49–57.
[25] Bonacci M, Lens S, Londoño MC, Mariño Z, Cid MC, Ramos-Casals M, et al. Virologic, clinical, and immune response outcomes of patients with Hepatitis C virus-associated cryoglobulinemia treated with direct-acting antivirals. Clin Gastroenterol Hepatol 2017;15:575–83.
[26] Davatchi F, Shahram F, Chams-Davatchi C, Shams H, Nadji A, Akhlaghi M, et al. Behcet's disease in Iran: analysis of 6500 cases. Int J Rheum Dis 2010;13:367–73.
[27] Jokar M, Mirfeizi Z. Epidemiology of vasculitides in Khorasan Province, Iran. Iran J Med Sci 2015;40:362–6.
[28] Joshi VR, Mittal G. Vasculitis-Indian perspective. J Assoc Physicians India 2006;54(Suppl):12–4.
[29] El Menyawi MM, Raslan HM, Edrees A. Clinical features of Behcet's disease in Egypt. Rheumatol Int 2009;29:641–6.
[30] El-Najjar AR, El-Soud AM, Amar HA, Diab MA. Clinical characteristics and disease activity of Behcet's disease patients in Zagazig, Eypt. The Egyptian Rheumatol 2015;37:191–6.
[31] Hussein MA, Ellawindi MI, Ragab G. Performance of classification criteria for Behcet's disease in an Egyptian cohort. Indian J Rheum 2017;12:152.
[32] Khabbazi A, Noshad H, Shayan FK, Kavandi H, Hajialiloo M, Kolahi S. Demographic and clinical features of Behcet's disease in Azerbaijan. Int J Rheum Dis 2014. http://dx.doi.org/10.1111/1756-185X.12512.
[33] Kobayashi S, Fujimoto S. Epidemiology of vasculitides: differences between Japan, Europe and North America. Clin Exp Nephrol 2013;17:611–4.
[34] Cao Y, Schmitz JL, Yang J, Hogan SL, Bunch D, Hu Y, et al. DRB1*15 allele is a risk factor for PR3-ANCA disease in African Americans. J Am Soc Nephrol 2011;l22:1161–1167.
[35] O'Donnell JL, Stevanovic VR, Frampton C, Stamp LK, Chapman PT. Wegener's granulomatosis in New Zealand: evidence for a latitude-dependent incidence gradient. Intern Med J 2007;37:242–6.
[36] Luqmani R. Assessment of disease activity and damage. In: Ball GV, Fessler BJ, Bridges SL Jr. (editors): Oxford Textbook of Vasculitis. Oxford University Press, Oxford, New York, third edition; 2014. p. 299–305.