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ORIGINAL ARTICLE

Characteristics, evolution, and outcome of patients with non-infectious uveitis referred for rheumatologic assessment and management: an Egyptian multicenter retrospective study

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Abstract

Objective To investigate the characteristics, evolution, and visual outcome of non-infectious uveitis.

Methodology Records of 201 patients with non-infectious uveitis (136 (67.7%) males and 84 (41.8%) juvenile-onset (≤ 16 years)) were retrospectively reviewed. Data were analyzed through Kruskal–Wallis and Mann–Whitney, chi-square (χ^2) tests, and logistic regression.

Results The median disease and follow-up durations were 36 (interquartile range (IQR) 24–70) and 24 (IQR 10–36) months, respectively. Fifty-eight (28.9%) patients had persistently idiopathic uveitis, and 143 (71.1%) were associated with rheumatic diseases, of whom uveitis heralded, coincided with, and succeeded the rheumatic manifestation(s) in 62/143 (43.4%), 37/143 (25.9%), and 44/143 (30.7%) patients, respectively. Established rheumatic diseases were Behçet's disease (103/201 (51.2%)), juvenile idiopathic arthritis (13/201 (6.5%)), sarcoidosis (8/201 (4%)), seronegative spondyloarthropathy (7/201 (3.5%)), and Vogt-Koyanagi-Harada (7/201 (3.5%)), and other diagnoses were present in 5/201 (2.5%) patients. Patients with idiopathic uveitis were characterized by a juvenile-onset ($p < 0.001$), lower male predominance ($p = 0.01$), prevalent granulomatous ($p < 0.001$), and anterior ($p = 0.001$) uveitis. The median visual acuity at last visit was 0.3 (IQR 0.05–0.6). Visual loss was present in 45/201 (22.3%) patients (36/201 (17.9%) unilateral and 9/201 (4.4%) bilateral). Apart from a longer disease duration ($p = 0.002$), lower educational level ($p = 0.03$), and prevalent panuveitis ($p < 0.001$), visual loss was not associated with any other studied ocular or extra-ocular characteristics.

Conclusion Behçet's disease (51.2%) and idiopathic uveitis (28.9%) were the most prevalent causes of non-infectious uveitis in our study. Visual loss (22.3%) was associated with a longer disease duration, lower education level, and prevalent panuveitis.

Key Points
- *Most common causes of uveitis referred to rheumatologists were Behçet's disease and idiopathic uveitis.*
- *Several rheumatic diseases initially presented only with uveitis, more commonly in adult and male patients.*
- *Panuveitis was more frequent among patients with an established rheumatic disease, whereas granulomatous uveitis was uncommon.*
- *Longer disease duration and presence of panuveitis were independently associated with visual loss.*

Keywords Behçet's disease · Idiopathic uveitis · Juvenile · Non-infectious uveitis · Outcome · Uveitis

Introduction

Inflammation of the uveal tract refers to an inflammatory process that can involve the iris, ciliary body, vitreous, choroid, and/or the retina [1]. Either it may be a part of systemic inflammatory disease or it can present as an isolated ocular inflammation [2].

Many underlying pathological mechanisms can predispose to uveitis such as infections and immune-mediated conditions

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[3]. Yet, the exact etiology remains unknown in about 30% of cases and hence termed "idiopathic" uveitis [4]. Immune-mediated uveitis could be associated with a myriad of autoimmune diseases including rheumatic diseases such as Behçet's disease (BD), spondyloarthritis (SpA), sarcoidosis, juvenile idiopathic arthritis (JIA), tubulointerstitial nephritis and uveitis (TINU) syndrome, and Vogt-Koyanagi-Harada (VKH) syndrome [5–7].

Interestingly, several determinates influence the characteristics and outcome of autoimmune uveitis such as socio-demographic factors, features of uveal involvement per se, and the extra-ocular characteristics of associated diseases [8]. Moreover, the disparity observed in the causes of uveitis across the globe could be attributed to geographic and racial factors, with reports from western countries demonstrating a high prevalence of SpA and sarcoidosis [2, 9–12]. On the other hand, BD is highly prevalent in Egypt [13–15] and various Middle Eastern countries [16–18] as they are along the silk route infamous for the high prevalence of BD [19]. It is of note that studies shedding light on autoimmune uveitis in particular are lacking in Egypt and the Middle East to the best of our knowledge. Moreover, limited studies worldwide [20, 21] have re-classified uveitis of an idiopathic onset to assess its potential evolution.

This study aimed at retrospectively characterizing non-infectious uveitis, classifying and re-classifying its course, and assessing its outcome among a cohort of patients referred for mutual rheumatologic and ophthalmologic management at three tertiary centers in Egypt.

Patients and methods

This retrospective cohort included the medical records of 201 patients with autoimmune uveitis being managed at Cairo, Benha, and Tanta University hospitals. Patients with co-existent infectious ocular or systemic involvement were excluded. The local ethics committee approved the study according to the principles of Declaration of Helsinki (Ethics committee approval serial number: R 1.7.2019).

Data collection

1. Socio-demographic characteristics: (i) age at the last recorded visit and onset were recorded, whereby the age at onset was determined at the age of development of initial ocular or extra-ocular manifestation(s). Juvenile-onset uveitis was determined at an age of ≤ 16 years; (ii) gender; (iii) disease duration: which was determined from the development of initial ocular or extra-ocular manifestation(s) till the last recorded visit, duration of follow-up, and number of follow-up visits; (iv) family history of uveitis, rheumatic, and/or systemic autoimmune diseases; (v) residency; (vi) education among the adult cohort was recorded and was classified according to the socio-economic status questionnaire for health research in Egypt [22].
2. Characteristics of uveitis were defined according to the Standardization of Uveitis Nomenclature (SUN) Working Group [23]. Accordingly, they were termed and persistent if they lasted for > 3 months and "limited" if they existed for < 3 months. The anatomical site was described as anterior, intermediate, posterior, or panuveitis. Granulomatous uveitis was considered if ophthalmic examination revealed keratic precipitates and/or iris nodules, granulomas in the choroid or optic nerve, while the uveitis was classified as "non-granulomatous" if these findings were absent.
3. In addition to ophthalmologic examination and subsequent imaging, several investigations were done to patients in our centers to exclude infectious causes of uveitis and to establish a rheumatic diagnosis. Laboratory investigations included the following: erythrocyte sedimentation rate, C-reactive protein, complete blood picture, differential count, liver transaminases, kidney and liver function tests, urine analysis, purified protein derivative skin test and when necessary QuantiFERON® Tuberculosis Gold test, syphilis and toxoplasma serology, and enzyme-linked immunosorbent assay for human immunodeficiency virus. Angiotensin-converting enzyme (ACE) and human leukocyte antigen-B27 (HLAB-27) typing were done when necessary. Radiologic investigations included baseline chest x-ray that was complimented with computed chest tomography when necessary and abdominal ultrasound. Imaging of the spine and sacroiliacs in the form of x-ray or magnetic resonance imaging was requested when indicated.
4. Diagnosis of the associated rheumatic diseases: Behçet's disease was diagnosed using the International Study Group Criteria of BD International criteria (ICBD) of 2014 [24]. Spondyloarthritis was classified according to the Assessment of SpondyloArthritis international Society (ASAS) for axial and peripheral SpA [25, 26]. International League of Associations for Rheumatology (ILAR) criteria were used for classification of JIA patients [27], whereas VKH syndrome was diagnosed using international revised criteria [28]. Confirmed diagnosis of sarcoidosis was established in the presence of histopathologic examination, whereas the diagnosis of suspected sarcoidosis was made in the presence of typical ocular findings and radiologic findings in concordance with sarcoidosis, with or without elevated angiotensin converting enzyme (ACE) [29]. Other rheumatic diagnoses were established according to the corresponding classification criteria.
5. Medications: Induction and maintenance medications implemented were recorded when available, with sequential

induction therapy being defined as the necessity to switch to an alternative induction agent owing to lack of response or worsening.

Outcome

- Visual outcome: Visual loss was defined and classified as follows: Moderate visual loss was diagnosed if visual acuity of the worse affected eye ranged from 0.5 to 0.2, and severe visual loss was diagnosed if it was ≤ 0.1. Complete blindness was defined as total vision loss (no perception of light), and those patients were further stratified into patients having unilateral or bilateral complete blindness to evaluate the magnitude and impact of severe visual disability as a visual outcome [30].
- Extra-ocular outcome was determined as complete response, 50% improvement, or lack of response

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 25 (IBM Corp., Armonk, NY, USA). Data were summarized using mean, standard deviation, median, minimum, and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Kruskal-Wallis and Mann-Whitney tests. For comparing categorical data, chi-square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. Odds ratio (OR) with 95% confidence intervals was calculated. p values less than 0.05 were considered as statistically significant.

Results

Baseline socio-demographic characteristics

This retrospective study included 201 patients with non-infectious uveitis, of whom 136 (67.7%) were males and 84 (41.8%) were juvenile-onset patients (≤ 16 years). The mean age at onset and the last visit was 21.8 ± 13.2 and 26.4 ± 14.3 years, respectively. The median disease and follow-up durations were 36 (interquartile range (IQR) 24–70) and 24 (IQR 10–36) months, respectively, with the median number of visits being 10 (IQR 5–22).

Data about residency was available for 144/201 (71.6%) patients, of whom 80/144 (55.6%) and 64/144 (44.4%) patients resided in rural and urban areas, respectively. Of the adults patients included (117/201), data about education was available for 96/117, with 29/96 (30.2%) and 34/96 (35.4%) patients being university and high school graduates, respectively, 25/96 (26%) could read and write, and 8/96 (8.3%) were illiterate. Interestingly, a family history of uveitis and a rheumatic disease was present in 4/163 (2.5%) and 13/163 (8%) patients, respectively.

Ocular and extra-ocular clinical characteristics

Characteristics of uveal involvement

The median time to diagnosis with uveitis was 1 (IQR 1–3) month. The site of uveal tract involvement varied to be anterior, intermediate, and posterior uveitis in 95 (47.3%), 6 (3%), and 31 (15.4%) patients, respectively, whereas panuveitis was present in 69 (34.3%) patients. Furthermore, uveitis was characterized by being unilateral, bilateral, and alternating in 43 (21.4%), 146 (72.6%), and 12 (6%) patients, respectively, and was granulomatous and associated with retinal vasculitis in 26 (12.9%) and 46 (22.9%) patients, respectively.

Pattern of onset of uveitis

Uveitis was the sole presenting manifestation in 120 (59.7%) patients (idiopathic-onset), whereas it coincided with rheumatic manifestation(s) in 44 (21.9%) patients (concurrent-onset) and followed the rheumatic diagnosis in 37 (18.4%) patients (subsequent-onset) (Fig. 1). There were several clinical and demographic differences according to the pattern of onset (Table 1).

Characteristics of persistently idiopathic uveitis

The term "idiopathic uveitis" was coined in about one-third of our cohort (58/201 (28.9%) patients), as no rheumatic or systemic diagnoses could be established by the last visit. Several differences were present between patients developing a rheumatic disease and those showing a persistently idiopathic course (Table 2).

Characteristics of rheumatic diseases

Of the studied cohort, a rheumatologic diagnosis was established by the last visit in 143 (71.1%) patients (Fig. 1). Further analysis of this subset of patients revealed that uveitis was of a concurrent-, subsequent-, and an idiopathic-onset in 37/143 (25.9%), 44/143 (30.7%), and 62/143 (43.4%) patients, respectively (Fig. 1).

The most prevalent rheumatic disease was BD being present in about half of our cohort (103/201 (51.2%)), followed by JIA (13/201 (6.5%)). The onset and course of uveitis and the rheumatic diagnoses established are illustrated in Fig. 1.

Interestingly, an idiopathic-onset evolved to be rheumatic-associated in about half of the patients initially presenting with

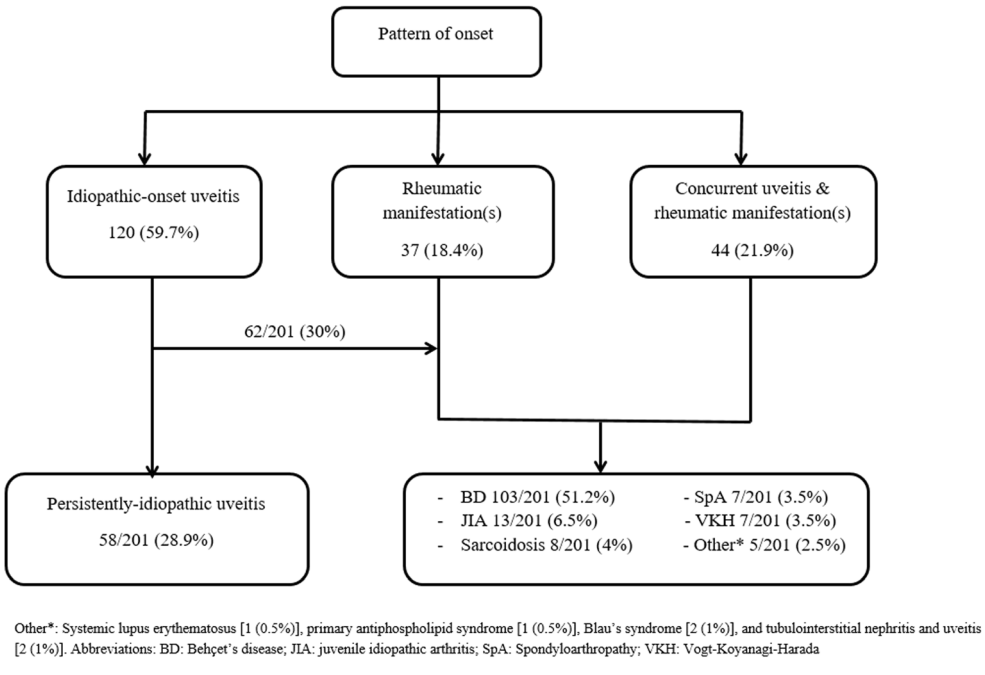

Fig. 1 Pattern of onset and course of uveitis in our cohort (201 patients)

Other*: Systemic lupus erythematosus [1 (0.5%)], primary antiphospholipid syndrome [1 (0.5%)], Blau's syndrome [2 (1%)], and tubulointerstitial nephritis and uveitis [2 (1%)]. Abbreviations: BD: Behçet's disease; JIA: juvenile idiopathic arthritis; SpA: Spondyloarthropathy; VKH: Vogt-Koyanagi-Harada

Table 1 Differences in the demographic and clinical characteristics according to the pattern of onset[¶,**]

	Idiopathic-onset uveitis $N = 120$ (%)	Subsequent-onset $N = 37$ (%)	Concurrent-onset $N = 44$ (%)	p value*
Demographic characteristics				
Age				
Juvenile-onset (≤ 16 years)	69 (57.5)	8 (21.6)	7 (15.9)	< 0.001
Adult-onset	51 (42.5)	29 (78.4)	37 (84.1)	
Gender				
Males	67 (55.8)	32 (86.5)	37 (84.1)	< 0.001
Females	53 (44.2)	5 (13.5)	7 (15.9)	
	Median (IQR) (months)			
Disease duration	26 (12–48)	60 (36–96)	60 (36–89)	< 0.001
Time to diagnosis with uveitis	1 (1–2)	4 (1.5–6)	1 (1–3)	0.04
Time to diagnosis with rheumatic disease	9.5 (3.5–21)	12 (3–36)	6 (1–12)	0.3
Characteristics of uveitis				
Site				
Anterior	64 (53.3)	16 (43.2)	15 (34.1)	0.04
Intermediate	3 (2.5)	1 (2.7)	2 (4.5)	
Posterior	13 (10.8)	11 (29.7)	7 (15.9)	
Panuveitis	40 (33.3)	9 (24.3)	20 (45.5)	
Granulomatous	24 (20)	1 (2.3)	1 (2.7)	0.001
Associated retinal vasculitis	24 (20)	11 (29.7)	11 (25)	0.4
Laterality				
Unilateral	29 (24.2)	9 (24.3)	5 (11.4)	0.3
Bilateral	84 (70)	25 (67.6)	37 (84.1)	
Alternating	7 (5.8)	3 (8.1)	2 (4.5)	
Course				
Number of flares (median (IQR))				
Ocular	2 (1–2)	2.5 (1–3)	2 (1–4)	0.07
Extra-ocular	0 (0–2)	3 (2–4)	2 (0–2)	0.001
Sequential induction	40/85 (47.1)	10/12 (83.3)	11/14 (78.6)	0.01

[¶] Unless indicated, data is presented in number and percentage, and unless indicated, data is derived from the total cohort

**Pattern of onset: described according to the timely association with rheumatic manifestation(s)

*Significant p value < 0.05

Table 2 Differences between patients with persistently idiopathic uveitis and rheumatic disease-associated[¶]

	Persistently idiopathic $N = 58$ (%)	Rheumatic disease-associated $N = 143$ (%)	p value*	OR	95% CI
Demographic characteristics					
Age					
Juvenile-onset (≤ 16 years)	45 (77.6)	39 (27.3)	< 0.001	9.2	4.5–18.9
Adult-onset	13 (22.4)	104 (72.7)			
Gender					
Males	32 (55.2)	104 (72.7)	0.01	2.1	1.1–4
Females	26 (44.8)	39 (27.3)			
	Median (IQR) (months)				
Disease duration	24 (12–48)	48 (24–72)	< 0.001	NA	NA
Time to diagnosis with uveitis	1 (1–2)	1 (1–3)	0.2	NA	NA
Characteristics of uveitis					
Site					
Anterior	40 (69)	55 (38.5)	0.001	NA	NA
Intermediate	1 (1.7)	5 (3.5)			
Posterior	4 (6.9)	27 (18.9)			
Panuveitis	13 (22.4)	56 (39.2)			
Granulomatous	17 (29.3)	9 (6.3)	< 0.001	0.1	0.06–0.3
Associated retinal vasculitis	5 (8.6)	41 (28.7)	0.002	4.2	1.5–11.4
Laterality					
Unilateral	16 (27.6)	27 (18.9)	0.3	NA	NA
Bilateral	38 (65.5)	108 (75.5)			
Alternating	4 (6.9)	8 (5.6)			
Course					
Number of ocular flares (median(IQR))	1.5 (1-2)	2 (1-3)	0.04	NA	NA
Necessity for sequential induction	23/49 (46.9)	38/62 (61.3)	0.1	NA	NA

Abbreviations: *NA* not applicable

[¶] Unless indicated, data is presented in number and percentage, and unless indicated, data is presented from the total cohort

*Significant p value < 0.05

isolated ocular involvement (62/120 (51.6%)), hence representing about a third of our studied cohort (62/201 (30.8%)), with the rheumatic diagnoses reached being BD (32/201 (16%)), sarcoidosis (8/201 (3.9%)), SpA (7/201 (3.4%)), VKH (7/201 (3.4%)), and JIA (5/201 (2.4%)), and other diagnoses were present in 3/201 (1.4%) patients, hence making all patients with sarcoidosis, SpA, and VKH in our cohort presenting with isolated ocular involvement.

Among patients with JIA, 11/13 (84.6%) were oligoarticular JIA, whereas polyarticular and systemic-onset JIA were present in one patient in each subgroup (1/13 (7.6%)). Among patients with SpA, 3/7 (42.8%) patients were diagnosed with ankylosing spondylitis, and 2/7 (28.5%) had inflammatory bowel disease, and 2/7 (28.5%) had psoriatic arthritis.

Mucocutaneous manifestations were the most prevalent extra-ocular involvement (105/143 (73.4%)), followed by musculoskeletal (42/143 (29.3%)), thrombotic (38/143 (26.5%)), neurologic (19/143 (13.2%)), gastrointestinal (6/143 (4.1%)), pulmonary (5/143 (3.4%)), and cardiac (5/143 (3.4%)) manifestations.

Gender differences

Male patients constituted the majority of our cohort (136 (67.7%) patients). They were characterized by a high prevalence of BD as opposed to female patients ($p < 0.001$) (Table 3).

Characteristics of uveitis according to the age of onset

Juvenile-onset patients (84 (41.8%)) were more inclined to have an idiopathic- onset ($p < 0.001$), which was further followed by a persistently idiopathic course ($p < 0.001$). Table 4 demonstrates the differences between adult- and juvenile-onset patients.

Table 3 Demographic and clinical characteristics according to gender[¶]

	Males $N = 136$ (%)	Females $N = 65$ (%)	p value*
Demographic characteristics			
Age (years)			
Juvenile-onset (≤ 16 years)	48 (35.3)	36 (55.4)	0.007
Adult-onset	88 (64.7)	29 (44.6)	
	Median (IQR) (months)		
Disease duration	48 (24–76)	36 (20–48)	0.02
Time to diagnosis with uveitis	1 (1–3)	1 (1–3)	0.9
Time to diagnosis with rheumatic disease	8 (3–24)	9 (3–18)	0.7
Clinical characteristics			
Rheumatic diagnosis reached			
BD	84 (61.8)	19 (29.2)	< 0.001
JIA	8 (5.9)	5 (7.7)	
Sarcoidosis	7 (5.1)	1 (1.5)	
SpA	4 (2.9)	3 (4.6)	
VKH	0	7 (10.8)	
Other	1 (0.7)	4 (6.2)	
None (persistently idiopathic uveitis)	32 (23.5)	26 (40)	
Characteristics of uveitis			
Site			
Anterior	62 (45.6)	33 (50.8)	0.009
Intermediate	5 (3.7)	1 (1.5)	
Posterior	28 (20.6)	3 (4.6)	
Panuveitis	41 (30.1)	28 (43.1)	
Granulomatous	15 (11)	11 (16.9)	0.2
Associated retinal vasculitis	34 (25)	12 (18.5)	0.3
Laterality			
Unilateral	30 (22.1)	13 (20)	0.9
Bilateral	98 (72.1)	48 (73.8)	
Alternating	8 (5.9)	4 (6.2)	
Course			
Number of flares (median(IQR))			
Ocular	2 (1–3)	2 (1–3)	0.9
Extra-ocular	1 (0–3)	1 (0–2)	0.3
Sequential induction	34/62 (54.8)	27/49 (55.1)	0.9
Extra-ocular outcome			
Complete improvement	63/76 (82.9)	19/28 (67.9)	0.08
50% response	13/76 (17.1)	7/28 (25)	
Non-responder	0	2/28 (7.1)	

Abbreviations: *BD* Behçet's disease, *JIA* juvenile idiopathic arthritis, *SpA* spondyloarthropathy, *VKH* Vogt-Koyanagi-Harada

[¶] Unless indicated, data is presented in number and percentage, and unless indicated is presented from the total cohort

*Significant p value < 0.05

Visual outcome

The median visual acuity in the worse eye attained by the last visit was 0.3 (IQR 0.05–0.6), with visual loss, the primary endpoint of our study, being present in 45/201 (22.3%) patients, whereby unilateral and bilateral visual losses were present in 36/201 (17.9%) and 9/201 (4.4%), respectively.

Several demographic and clinical factors were associated with visual loss (Table 5), yet with no association with the

Table 4 Demographic and clinical characteristics according to the age of onset[¶]

	Juvenile-onset (≤ 16 years) *N* = 84 (%)	Adult-onset (> 16 years) *N* = 117 (%)	*p* value*
Demographic characteristics			
Gender			
Males	48 (57.1)	88 (75.2)	0.007
Females	36 (42.9)	29 (24.8)	
	Median (IQR) (months)		
Disease duration	26 (12–48)	48 (24–84)	< 0.001
Time to diagnosis with uveitis	1 (1–3)	1 (1–2)	0.7
Time to diagnosis with rheumatic disease	6 (2–12)	12 (3–24)	0.1
Clinical characteristics			
Rheumatic diagnosis reached**			
BD	7/71 (9.9)	96/117 (82.1)	< 0.001
Sarcoidosis	7/71 (9.9)	1/117 (0.9)	
SpA	2/71 (2.8)	5/117 (4.3)	
VKH	7/71 (9.9)	0	
Other	3/71 (4.2)	2/117 (1.7)	
None (persistently idiopathic)	45/71 (63.4)	13/117 (11.1)	
Characteristics of uveitis			
Site			
Anterior	53 (63.1)	42 (35.9)	< 0.001
Intermediate	0	6 (5.1)	
Posterior	6 (7.1)	25 (21.4)	
Panuveitis	25 (29.8)	44 (37.6)	
Granulomatous	23 (27.4)	3 (2.6)	< 0.001
Associated retinal vasculitis	8 (9.5)	38 (32.5)	< 0.001
Laterality			
Unilateral	14 (16.7)	29 (24.8)	0.04
Bilateral	68 (81)	78 (66.7)	
Alternating	2 (2.4)	10 (8.5)	
Course			
Number of flares (median (IQR))			
Ocular	1 (1-2)	2 (1-4)	0.007
Extra-ocular	1 (0–2)	2 (0–2)	0.9
Sequential induction	37/68 (54.4)	24/43 (55.8)	0.8
Extra-ocular outcome			
Complete improvement	14/27 (51.9)	68/79 (86.1)	< 0.001
50% response	11/27 (40.7)	9/79 (11.4)	
Non-responder	2/27 (7.4)	2/79 (2.5)	

Abbreviations: *BD* Behçet's disease, *SpA* spondyloarthropathy, *VKH* Vogt-Koyanagi-Harada

[¶] Unless indicated, data is presented in number and percentage, and unless indicated is presented from the total cohort

*Significant p value < 0.05

**Juvenile idiopathic arthritis was excluded from the comparison, with the other diagnoses being evaluated in 71 juvenile-onset patients

prevalence of an idiopathic-onset uveitis ($p = 0.07$) or diagnosis established, whether persistently idiopathic- or rheumatic-associated ($p = 0.3$).

Discussion

The underlying etiology of uveitis, a potentially sight-threatening and disabling condition, is variable and complex. Autoimmune uveitis is distinctly of a multifaceted nature as it could be influenced by several interrelated features such as geographic [11], racial [31], and socio-economic [32] parameters. Yet to the best of our knowledge, studies from Egypt [13–15] and the Middle East [16–18, 33, 34] have not addressed non-infectious uveitis as a separate entity.

Our aim, through excluding infectious causes of uveitis, was to present cases that necessitate mutual rheumatologic and ophthalmologic assessment, diagnosis, treatment, and follow-up. Furthermore, we hypothesize that isolated ocular involvement could herald several rheumatic diseases and hence need constant follow-up and re-evaluation.

Table 5 Differences between patients with and without visual loss[¶]

	Visual loss $N = 45$ (%)	Absent visual loss $N = 156$ (%)	p value*	OR	95% CI
Socio-demographic characteristics					
Age at onset					
Juvenile (≤ 16 years)	19 (42.2)	65 (41.7)	0.9	NA	NA
Adult	26 (57.8)	91 (58.3)			
Gender					
Males	30 (66.7)	106 (67.9)	0.8	NA	NA
Females	15 (33.3)	50 (32.1)			
Education**					
University	5/19 (26.3)	24/77 (31.2)	0.03	NA	NA
High school	10/19 (52.6)	24/77 (31.2)			
Read and write	1/19 (5.3)	24/77 (31.2)			
Illiterate	3/19 (15.8)	5/77 (6.5)			
Residence					
Urban	12/26 (46.2)	52/118(44.1)	0.8	NA	NA
Rural	14/26 (53.8)	66/118 (55.9)			
	Median (IQR)				
Disease duration (months)	50 (36–72)	36 (16–60)	0.002	NA	NA
Duration of follow-up (months)	17 (11–36)	24 (10–36)	0.9	NA	NA
Number of visits	10.5 (5–19)	10 (5–22)	0.7	NA	NA
Time to diagnosis with uveitis (months)	1 (1–3)	1 (1–3)	0.7	NA	NA
Time to diagnosis with the rheumatic disease (months)	12 (2–24)	6 (3–21)	0.4	NA	NA
Clinical characteristics					
Initial onset					
Idiopathic	25 (55.6)	95 (60.9)	0.07	NA	NA
Concurrent	15 (33.3)	29 (18.6)			
Subsequent	5 (11.1)	32 (20.5)			
Rheumatic diagnosis reached by the last visit					
None (persistently idiopathic uveitis)	14 (31.1)	44 (28.2)	0.3	NA	NA
BD	27 (60)	76 (48.7)			
JIA	2 (4.4)	11 (7.1)			
Sarcoidosis	0	8 (5.1)			
SpA	0	7 (4.5)			
VKH	2 (4.4)	5 (3.2)			
Others	0	5 (3.2)			
Characteristics of uveitis					
Site					
Anterior	14 (31.1)	81 (51.9)	< 0.001	NA	NA
Intermediate	3 (6.7)	3 (1.9)			
Posterior	2 (4.4)	29 (18.6)			
Panuveitis	26 (57.8)	43 (27.6)			
Laterality					
Unilateral	7 (15.6)	36 (23.1)	0.2	NA	NA
Bilateral	37 (82.2)	109 (69.9)			
Alternating	1 (2.2)	11 (7.1)			
Granulomatous	2 (4.4)	24 (15.4)	0.05	0.2	0.05–1.1
Associated retinal vasculitis	14 (31.1)	32 (20.5)	0.1	1.7	0.8–3.6
Treatment					
Induction agents					
Azathioprine	10/32 (31.3)	44/127 (34.6)	0.6	NA	NA
Methotrexate	12/32 (37.5)	48/127 (37.8)			

Table 5 (continued)

	Visual loss $N = 45$ (%)	Absent visual loss $N = 156$ (%)	p value*	OR	95% CI
Anti-TNF	4/32 (12.5)	9/127 (7.1)			
Cyclosporine	4/32 (12.5)	11/127 (8.7)			
Cyclophosphamide	2/32 (6.3)	15/127 (11.8)			
Sequential induction	19/27 (70.4)	42/84 (50)	0.06	2.3	0.9–6
Maintenance					
Azathioprine	12/29 (41.4)	55/117 (47)	0.3	NA	NA
Methotrexate	2/29 (6.9)	20/117 (17.1)			
Anti-TNF	12/29 (41.4)	28/117 (23.9)			
Cyclosporine	2/29 (6.9)	7/117 (6)			
Combination	1/29 (3.4)	7/117 (6)			
Course					
Number of flares (median (IQR))					
Ocular	2 (1–4)	2 (1–3)	0.1	NA	NA
Extra-ocular	2 (1–3)	1 (0–2)	0.03	NA	NA
Extra-ocular improvement					
Complete	15/21 (71.4)	67/85 (78.8)	0.4	NA	NA
50% improvement	5/21 (23.8)	17/85 (20)			
Non-responder	1/21 (4.8)	1/85 (1.2)			

Abbreviations: *NA* not applicable, *IQR* interquartile range, *Anti-TNF* anti-tumor necrosis factor, *BD* Behçet's disease, *JIA* juvenile idiopathic arthritis, *SpA* spondyloarthropathy, *VKH* Vogt-Koyanagi-Harada

¶ Unless indicated, data is presented in number and percentage, and unless indicated, data is derived from number of total patients

*Significant $p < 0.05$

**Education has been presented from the number of adult patients with available data about education

There were several differences and similarities between our cohort and other cohorts in the Middle East (Supplementary Table 1). In this study, the majority of our patients had rheumatic disease-associated uveitis (71.1%), with the most prevalent rheumatic diagnosis being BD (51.2%). Similarly, BD was the most common cause of non-infectious uveitis in previous reports from Egypt [13, 14], Iran [33], and Turkey [17], as they are along the silk route characterized by a high prevalence of BD [19]. On the other hand, SpA and HLA-B27-associated uveitis are the leading causes of uveitis in Western countries [2, 9–12].

Although JIA was the second most prevalent rheumatic disease-associated uveitis (13/201 (6.5%)), the second most prevalent form of uveitis in our cohort, following BD (103/201 (51.2%)), was idiopathic (58/201 (28.9%)), and these findings are similar to the frequency of idiopathic uveitis demonstrated in previous studies from Egypt [13, 14] and the Middle East [16–18, 34]. It is of note that we have retrospectively tracked the onset and course of what is so-called idiopathic uveitis and detected that an idiopathic-onset uveitis has evolved into a rheumatic-associated one in 62/201 (30.8%) patients, leaving a substantial majority of patients (58/201 (28.9%)) with isolated autoimmune ocular inflammation or what we have labeled as "persistently" idiopathic uveitis. Hence, uveitis could herald several rheumatic diseases, with 31% (32/103) of our BD and 38.4% (5/13) of our JIA patients showing an idiopathic-onset, and interestingly, all SpA, sarcoidosis, and VKH patients in our cohort had an idiopathic-onset.

To the best of our knowledge, data re-classifying idiopathic uveitis in the Middle East is lacking, whereas a previous study from the USA reported that a subsequent diagnosis was fulfilled in 29% of their patients presenting with an idiopathic-onset [20], with sarcoidosis (36.5%) being the most common subsequent diagnosis, followed by HLA-B27-associated uveitis (21.1%).

It is of note that due to the retrospective nature of our study, data available about HLA-B27 was rather scarce being tested in 43/201 (21.3%) of our cohort; of whom 4/43 patients were positive (9.3%); hence, subanalyses were not feasible. Interestingly, however, a previous study assessing the prevalence of HLA-B27 in the Middle East and Africa among the normal population and patients with SpA demonstrated a rather low prevalence [35]. Moreover, several Egyptian [13, 14] and Middle Eastern studies [18, 36] demonstrated a low prevalence of HLA-B27 associated uveitis among their included non-infectious causes.

Among the demographic characteristics studied, patients with persistently idiopathic uveitis showed a less pronounced male predominance ($p = 0.01$) and had a juvenile-onset more commonly ($p < 0.001$). Moreover, idiopathic uveitis was most commonly anterior ($p = 0.001$) and granulomatous

($p < 0.001$), raising the possibility of eventually evolving to rheumatic diseases frequently associated with anterior or granulomatous uveitis such as SpA and sarcoidosis [20].

Therefore, the nature of the underlying autoimmune disease, whether systemic or ocular, could be considered as one of the leading factors affecting the anatomical diagnosis and the pattern and nature of uveal tract inflammation. The most common anatomical diagnosis of uveitis in our study was anterior (47.3%), followed by panuveitis (34.3%). Anterior [15] and panuveitis [13, 14] were the most sites of uveal tract inflammation in previous Egyptian studies.

Upon evaluating the characteristics of non-infectious uveitis according to age and gender, juvenile-onset patients (41.8% (84/201 patients)]) were characterized by a high prevalence of anterior ($p < 0.001$) and granulomatous ($p < 0.001$) uveitis and lower prevalence of co-existing retinal vasculitis ($p < 0.001$), which could be a reflection to the high prevalence of idiopathic-onset and persistently idiopathic uveitis among this age group rather than rheumatic disease–associated uveitis ($p < 0.001$). Interestingly, male patients were characterized by having a higher prevalence of rheumatic-associated diseases with BD being the most prevalent rheumatic diagnosis ($p < 0.001$).

The ultimate goal of investigating the characteristics of non-infectious uveitis is assessing its outcome, with the outcome in our study being visual loss. Visual loss was present in 45/201 (22.3%) patients. Apart from education that was characterized by a higher prevalence of illiteracy among patients with visual loss ($p = 0.03$), there was no association with any of the socio-demographic characteristics recorded. The association of demographic findings with visual loss has been inconsistent across various studies, with a previous study from the USA [12] showing that female patients and those with a younger age of onset were more inclined to have a favorable visual outcome, whereas another study from the Netherlands [37] found no association between visual outcome and various demographic characteristics.

Apart from a higher prevalence of panuveitis among patients with visual loss ($p < 0.001$), there was no association with the visual outcome with any of the other studied characteristics of uveitis. Non-anterior uveitis was associated with a poor visual outcome in a previous study [11], while the site of uveitis showed no association with the visual outcome in another [37].

The main limitation of our study resides in its retrospective nature, which led to some missing data and to the inability to include several features, including nature of onset (acute/chronic/relapsing) and social information such as health care source and occupation. Moreover, its retrospective nature did not enable us to test HLA-B27 on a wide scale and hence potentially reflect its true prevalence. Furthermore, despite the substantial number of medical records included, there were no reported cases of vasculitis-associated uveitis in our cohort that could have been detected if the study included a larger cohort. On the other hand, our multicenter and multidisciplinary study has many strengths, as it retrospectively tracked the course of uveitis with an idiopathic-onset, which interestingly evolved into several rheumatic diseases, an angle that to the best of our knowledge was yet to be investigated in the Middle East.

In conclusion, in our cohort that was characterized by exclusion of infectious uveitis, BD was the most underlying cause of uveitis, followed by persistently idiopathic uveitis. An idiopathic-onset uveitis heralded several rheumatic diseases. Persistently, idiopathic uveitis showed a female predominance and was more common among those with a juvenile-onset. Moreover, it was mostly anterior, granulomatous, and less commonly associated with retinal vasculitis. Apart from a longer disease duration, lower educational level, higher prevalence of panuveitis, and more frequent extra-ocular flares among patients with visual loss, there was no association with any of the studied socio-demographic, other ocular or extra-ocular characteristics, or the implemented induction or maintenance treatment regimens.

Compliance with ethical standards

The local ethics committee approved the study according to the principles of Declaration of Helsinki (Ethics committee approval serial number: R 1.7.2019).

Disclosures None.

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