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ORIGINAL PAPER

Incidence and changing patterns of uveitis in Central Tokyo

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Abstract

Purpose The patterns of uveitis in Tokyo have recently changed due to advances in examination tools. We aimed to investigate the changes in the patterns of uveitis between 2004–2015 and 2016–2018.

Methods We retrospectively reviewed the data of 732 patients who visited the Uveitis Clinic at the University of Tokyo Hospital between January 2016 and December 2018. Background characteristics, laboratory results, and imaging findings were analysed. We compared the incidences of uveitis in 2016–2018 and 2004–2015 to identify changes in the patterns.

Results The most frequent diagnoses were sarcoidosis (8.9%), herpetic iridocyclitis (6.7%), intraocular lymphoma (5.5%), Vogt–Koyanagi–Harada disease (4.8%), unclassified acute anterior uveitis (4.6%), Behçet's disease (4.5%), bacterial endophthalmitis (2.9%), and Posner-Schlossman syndrome (2.6%). Suspected sarcoidosis (20.9%) was the most common cause of unclassified uveitis. The incidence of intraocular lymphoma was significantly higher in 2016–2018 than in 2004–2015. Between 2004 and 2018, herpetic iridocyclitis, bacterial endophthalmitis, and juvenile chronic iridocyclitis exhibited an increasing trend, and the incidences of Posner-Schlossman syndrome, unclassified acute anterior uveitis, Behçet's disease, and Vogt–Koyanagi–Harada disease exhibited a decreasing trend.

Conclusion The changing patterns of uveitis were characterised by increases in the incidence of intraocular lymphoma. This may be attributed to recent advances in examination tools, the changes in the referred patient population, and the aging Japanese population.

Keywords Uveitis · Diagnosis · Incidence · Japan · Trend

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Background

Uveitis is a major cause of vision loss in developed countries [1]. It is one of the major causes of preventable blindness [2, 3] and severely affects the quality of life [4]. The distributions of the types and aetiologies of uveitis vary worldwide and are believed to be affected by genetic, ethnic, geographic, environmental, and lifestyle factors [5–10]. As a result, the patterns of uveitis vary greatly according to the population and the time of research. For example, one report from Taiwan revealed that the incidences of herpetic anterior uveitis, acute retinal necrosis, and cytomegalovirus (CMV) retinitis have recently increased, while those of toxoplasmosis and tuberculosis have decreased [11], compared to the results of a previous study [12]. Therefore, it is vital to analyse the epidemiology of this disease in various regions over a long period of time.

Currently, new examination tools for the diagnosis of uveitis, including interferon-gamma release assays; polymerase chain reaction (PCR) analysis for infectious agents using aqueous samples [13]; and multimodal imaging using optical coherence tomography (OCT), OCT angiography, and fundus autofluorescence [7, 14] have been developed to aid clinicians in the differential diagnosis of uveitis. Consequently, the number of definitive diagnoses of uveitis has been steadily increasing in Japan [15, 16]. However, approximately 30–40% of new patients with uveitis did not receive a definite diagnosis in a recent study [16].

Region-specific information regarding the patterns of uveitis is useful when diagnosing new patients, and there have been many reports on this topic from Japan as well as various other countries [2, 3, 8, 11, 12, 15–26]. Previously, we examined the long-term patterns of uveitis in new patients at the University of Tokyo Hospital between 1963 and 2015 [17–19] and concluded that the patterns of uveitis in Tokyo were changing rapidly in a short period of time because of advances in the examination tools for diagnosing uveitis. Therefore, up-to-date information regarding the patterns of uveitis in new patients is vital, and we believe that the data from our hospital are representative of the changing patterns of uveitis in Japan.

In the current study, we aimed to determine the incidence of uveitis from 2016–2018 and identify recent changes in the patterns of uveitis.

Methods

Patients and data collection

This study aimed to determine the incidence of uveitis between 2016 and 2018 and identify changes in its patterns. We retrospectively investigated the clinical records of 732 patients (333 men, 399 women) with uveitis who first visited the Uveitis Clinic of the University of Tokyo Hospital, a tertiary referral centre located in central Tokyo, between January 2016 and December 2018. Patients who had been diagnosed prior to 2016 but did not have active intraocular inflammation during 2016–2018 were excluded.

We extracted clinicodemographic data, including age, sex, diagnosis, anatomic location of inflammation, laboratory test results of blood and urine, and chest X-ray and fluorescein fundus angiography findings from the patients' medical records.

Diagnosis of uveitis

We adopted the classification of uveitis used in a nationwide survey of uveitis conducted in 2009 in Japan [16]. The anatomic diagnosis was assessed according to the classification of the Standardization of Uveitis Working Group as anterior uveitis, intermediate uveitis, posterior uveitis, or panuveitis [27]. Our diagnostic methods for uveitis have been described previously [19]. Briefly, patients with uveitis underwent screening blood tests, urine tests, chest X-ray examination, and the Mantoux reaction test at the initial presentation. Furthermore, when infectious origin was suspected, an aqueous tap or vitrectomy was performed to collect a vitreous sample. Then, quantitative PCR analysis for uveitis-causing infectious agents, including herpes simplex virus (HSV), varicella zoster virus (VZV), and CMV [14], and microscopic examinations and cultures for bacteria were performed using ocular samples. Unilateral, granulomatous inflammation, iris atrophy, increased intraocular pressure during inflammation, and decreased number of corneal endothelial cell compared to that in the opposite eye were considered

indicative of herpetic iridocyclitis. When any of these clinical features were present, anterior chamber tap for PCR test was recommended and performed when the patient agreed. When obvious skin lesions characteristic of herpes zoster ophthalmicus were observed, a diagnosis of VZV iridocyclitis was made without performing a PCR test. The diagnostic criteria for Posner-Schlossman syndrome were 'repeated high intraocular pressure, mild anterior ocular inflammation, neither skin or corneal lesions characteristic of HSV or VZV, and at least one negative result for PCR test for herpesviruses, including CMV'. We diagnosed Fuchs heterochromic iridocyclitis according to the clinical diagnostic criteria reported in a previous study [28].

Blood cultures, serum β-D-glucan, interferon-gamma release assays, and human leukocyte antigen (HLA) typing were performed for suspected bacterial/fungal endophthalmitis, tuberculous uveitis, acute anterior uveitis, or Behçet's disease. Moreover, vitreous fluid investigations were carried out in cases of suspected intraocular lymphoma. We diagnosed Behçet's disease [29], sarcoidosis [30], Vogt–Koyanagi–Harada disease (VKH) [31], and presumed tuberculous uveitis [32] according to the diagnostic criteria for each disease. The diagnostic criteria of definite and presumed ocular sarcoidosis reported by the International Workshop on Ocular Sarcoidosis (IWOS) [30] were used for the definitive diagnosis of ocular sarcoidosis in this study. Conversely, the patients who did not meet the IWOS criteria for definite or presumed ocular sarcoidosis but met those of ocular clinical signs for probable ocular sarcoidosis (3 or more out of 7) [30] were suspected of having sarcoidosis in this study. Intraocular lymphoma was diagnosed when at least two of the following four criteria were met [19]: (1) cytology grade > 3; (2) interleukin (IL)-10/IL-6 concentration ratio > 1 or IL-10 level > 50 pg/mL in the intraocular fluid [33]; (3) light chain restriction by flow cytometry [34]; and (4) positive PCR results for immunoglobulin heavy chain gene rearrangement [34]. Regarding acute anterior uveitis, patients with unique systemic symptoms of ankylosing spondylitis, ulcerative colitis, or psoriasis were diagnosed with systemic disease-associated uveitis. Those with HLA-B27 were diagnosed with HLA-B27-associated acute anterior uveitis. Patients who were negative for HLA-B27 and developed acute onset iridocyclitis accompanied with highly viscous fibrin in the anterior chamber during an attack [35] were diagnosed as having unclassified acute anterior uveitis. Human T lymphotropic virus type-1 [36], diabetic iritis [37], acute zonal occult outer retinopathy [38], and juvenile chronic iridocyclitis [39] were diagnosed based on the typical ocular findings and clinical courses, as described in the respective previous reports.

Patterns in uveitis

We calculated the incidences of causative diseases for uveitis in new patients between 2016 and 2018 and compared the results with our previously reported findings (2004–2015) [17–19].

Statistical analysis

The proportions of patients with uveitic diseases in previous studies (2004–2015) and those of the current study (2016–2018) were compared statistically and are presented in Table 1. A significant increase in the incidence of a particular uveitic disease was determined by the chi-square test, by comparing the proportion of one uveitic disease with those of all other uveitic diseases over two study periods (between 2016–2018 and 2012–2015, 2016–2018, and 2004–2015). Statistical analyses were performed using GraphPad Prism for Windows (version 8; GraphPad Software Inc., La Jolla, CA, USA). A p-value < 0.0019 was considered statistically significant by Bonferroni correction.

Results

A total of 732 new patients (men: n = 333, women: n = 399) with uveitis were treated at our institution between 2016 and 2018. Their mean age was 56.4 ± 19.0 years (men: 57.2 ± 17.6 years; women: 55.7 ± 20.0 years). The most frequent age range was 60–69 years in both men and women (Fig. 1). Among these 732 patients, 449 (61.3%) received a definitive diagnosis of uveitis (Table 2). The most frequent diagnosis was sarcoidosis (n = 65, 8.9%), followed by herpetic iridocyclitis because of HSV, VZV, and CMV (n = 49, 6.7%) and intraocular lymphoma (n = 40, 5.5%). Six of the 16 cases of HLA-B27-associated acute anterior uveitis had ankylosing spondylitis.

Table 1 Shifts in the number and distribution of uveitis cases (2004–2018)

	2004–2006	2007–2009	2010–2012	2013–2015	2016–2018	*p*-value[a]	2004–2015	*p*-value[b]
New patients (*n*)	426	535	695	750	732		2406	-
Diagnosis, n (% of new patients)								
Herpetic iridocyclitis	20 (4.7)	28 (5.2)	38 (5.5)	56 (7.5)	49 (6.7)	0.5622	142 (5.9)	0.4325
Sarcoidosis	40 (9.4)	47 (8.9)	60 (8.6)	53 (7.1)	65 (8.9)	0.1974	200 (8.3)	0.6289
Behçet's disease	21 (4.9)	26 (4.9)	32 (4.6)	33 (4.4)	33 (4.5)	0.9196	112 (4.7)	0.8684
Vogt–Koyanagi–Harada disease	27 (6.3)	37 (6.9)	28 (4.0)	31 (4.1)	35 (4.8)	0.5454	123 (5.1)	0.7201
Intraocular lymphoma	4 (0.9)	13 (2.4)	21 (3.0)	31 (4.1)	40 (5.5)	0.1868	69(2.9)	0.001
Posner-Schlossman syndrome	19 (4.5)	20 (3.7)	25 (3.6)	25 (3.3)	19 (2.6)	0.4029	89 (3.7)	0.1516
Bacterial endophthalmitis	2 (0.5)	10 (1.9)	13 (1.9)	23 (3.1)	21 (2.9)	0.8225	48 (2.0)	0.158
Fuchs heterochromic iridocyclitis	9 (2.1)	10 (1.9)	11 (1.6)	20 (2.7)	17 (2.3)	0.6711	50 (2.1)	0.6889
HLA-B27-associated AAU	11 (2.6)	14 (2.6)	13 (1.9)	16 (2.1)	16 (2.2)	0.9446	54 (2.2)	0.9251
Unclassified AAU	19 (4.5)	30 (5.6)	48 (6.9)	42 (5.6)	34 (4.6)	0.4046	139 (5.8)	0.2398
Juvenile chronic iridocyclitis	3 (0.7)	7 (1.3)	11 (1.6)	17 (2.3)	14 (1.9)	0.6339	38 (1.6)	0.5364
Other	107 (25.1)	153 (28.6)	170 (24.5)	135 (18.0)	106 (14.5)	0.0664	565 (23.5)	< 0.0001
Unclassified uveitis	125 (29.3)	140 (26.2)	225 (32.4)	268 (35.7)	283 (38.7)	0.2436	758 (31.5)	0.0003

2004–2018 data [17–19]

[a]Chi-square test comparing the numbers of cases between 2013–2015 and 2016–2018

[b]Chi-square test comparing the numbers of cases between 2004–2015 and 2016–2018

Patients with herpetic iridocyclitis were categorised into five groups according to the reason for diagnosis, as previously described [19]. CMV-DNA positivity was the most common reason (n = 29, 59.2%), followed by skin lesions of herpes zoster ophthalmicus (n = 10, 20.4%), HSV-DNA positivity (n = 5, 10.2%), VZV-DNA positivity (n = 4, 8.2%), and HHV7-DNA positivity (n = 1, 2.0%) (Table 3).

Seventeen cases met the criteria for clinical diagnosis of Fuchs heterochromic iridocyclitis. We measured the Goldmann–Witmer coefficient for antibody against rubella virus (Q values) [40] in 12 cases, of which values of $Q > 3$ were found in four cases. In addition, we performed herpes virus PCR examination in five of the 17 cases, which were all negative.

Table 4 indicates the distributions of patients with uveitis across three age groups (< 20 years, 20–59 years, and ≥ 60 years). In these patients, juvenile chronic iridocyclitis, Behçet's disease, and sarcoidosis were the most frequent diagnoses, respectively. Definitive diagnoses were not made for the remaining 283 patients (38.7%). Among these patients, suspected sarcoidosis was the most common diagnosis (n = 153, 20.9%), which accounted for 54.1% of all suspected diagnoses.

Table 5 presents the distribution of uveitis according to the anatomic classification (anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis). In this study, 242 of 732 patients (33.1%) had anterior uveitis, 11 (1.5%) had intermediate uveitis, 52 (7.1%) had posterior uveitis, and 427 (58.3%) had panuveitis. The distribution of uveitis according to the anatomic site did not markedly differ from that observed in our previous studies [17–19].

Table 1 indicates the shifts in the numbers and distributions of cases of uveitis diagnosed at the University of Tokyo Hospital over a 15-year period [17–19]. Compared to the findings of our previous study on the patterns of uveitis between 2013 and 2015 [19], there was no significant difference in the numbers of cases of specific uveitis diseases. However, we observed increasing trends in the incidences

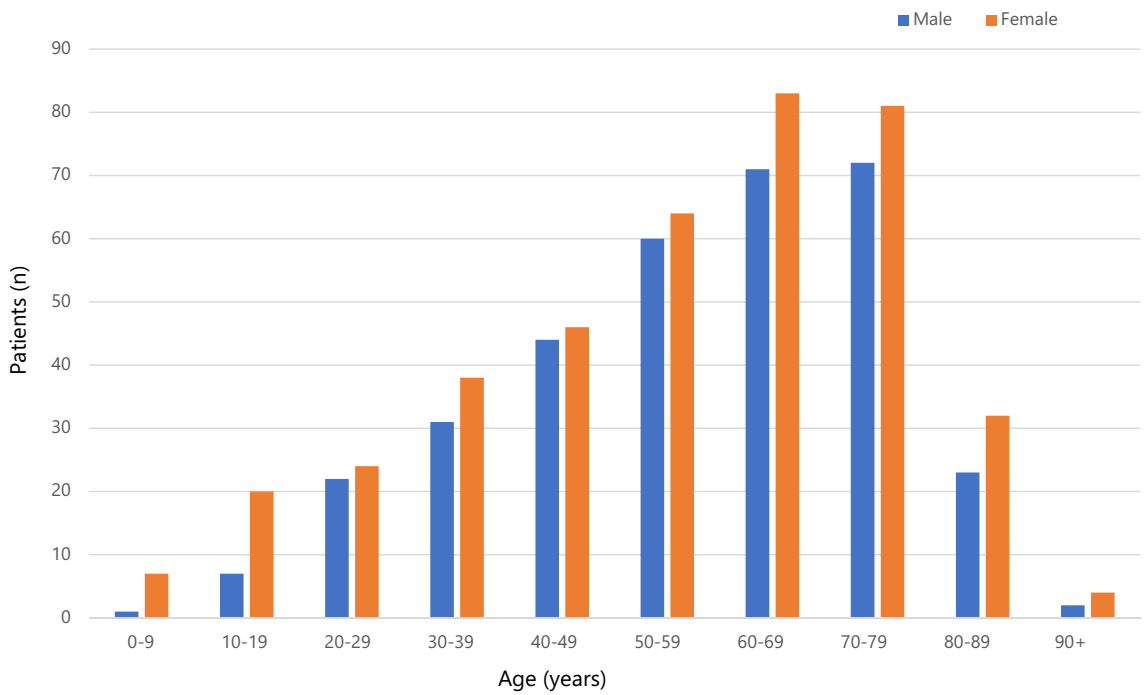

Fig. 1 Distribution of uveitis between 2016 and 2018 according to age and sex. Uveitis was most frequent among men and women aged 60–79 years

of sarcoidosis, VKH, and intraocular lymphoma in the past 3 years. In contrast, herpetic iridocyclitis, Posner-Schlossman syndrome, bacterial endophthalmitis, Fuchs heterochromatic iridocyclitis, unclassified acute anterior uveitis, and juvenile chronic iridocyclitis exhibited a decreasing trend. Compared to the findings of our previous studies on the uveitis patterns between 2004 and 2015 [17–19], the present analysis indicated that intraocular lymphoma ($p = 0.001$) and unclassified uveitis ($p = 0.0003$) significantly increased in the past 3 years. There were no significant differences in the patterns of other uveitis diseases, but we observed that the incidences of herpetic iridocyclitis, bacterial endophthalmitis, and juvenile chronic iridocyclitis exhibited an increasing trend throughout the 15-year period (2004–2018). Further, the incidences of Posner-Schlossman syndrome, unclassified acute anterior uveitis, Behçet's disease, and VKH exhibited a decreasing trend during this period.

Table 6 presents the distributions of age at the first visit in this study (2016–2018) and in previous studies (2004–2006, 2007–2009, 2010–2012, and 2013–2015). The average age exhibited a gradual increasing trend.

Discussion

The current study demonstrated that the incidences of intraocular lymphoma in new patients with uveitis significantly increased in 2016–2018 compared to 2004–2015 [17–19]. Moreover, the incidences of herpetic iridocyclitis, bacterial endophthalmitis, and juvenile chronic iridocyclitis gradually increased over a 15-year period (2004–2018). In contrast, the incidences of Posner-Schlossman syndrome, unclassified acute anterior uveitis, Behçet's disease, and VKH decreased during this period. One possible reason for the increasing trend in herpetic iridocyclitis and intraocular lymphoma is the aging Japanese population [41]. Indeed, the average age of new patients with uveitis at our hospital is gradually increasing: the average age of patients with uveitis in the current study (2016–2018) was 3.2 years higher than that in 2004–2006 [17]. Further, the average ages of patients with herpetic iridocyclitis and intraocular lymphoma in the current study were 62.0 ± 15.3 years and 67.1 ± 12.7 years, respectively. However, the mean age at the onset of anterior uveitis associated with herpes virus was > 55 years in a Japanese study [42];

Table 2 Distribution of uveitis among new patients (2016–2018)

	Patients (*n*)		Sex	
	n	%	Male	Female
Total	732	100.0	333	399
Diagnosis				
Sarcoidosis	65	8.9	21	44
Herpetic iridocyclitis	49	6.7	33	16
Intraocular lymphoma	40	5.5	21	19
Vogt–Koyanagi–Harada disease	35	4.8	20	15
Unclassified AAU	34	4.6	13	21
Behçet's disease	33	4.5	14	19
Bacterial endophthalmitis	21	2.9	17	4
Posner-Schlossman syndrome	19	2.6	13	6
Fuchs heterochromic iridocyclitis	17	2.3	10	7
HLA-B27-associated AAU	16	2.2	6	10
Juvenile chronic iridocyclitis	14	1.9	3	11
Cytomegalovirus retinitis	12	1.6	9	3
Tuberculosis	10	1.4	4	6
Fungal endophthalmitis	9	1.2	6	3
Acute retinal necrosis	8	1.1	6	2
MEWDS	6	0.8	0	6
Iridocyclitis because of RA	4	0.5	2	2
Psoriatic uveitis	4	0.5	4	0
TINU	4	0.5	0	4
PIC	3	0.4	1	2
AZOOR	3	0.4	1	2
APMPPE	3	0.4	2	1
Systemic lupus erythematosus	3	0.4	1	2
Sclerouveitis because of scleroderma	3	0.4	0	3
Toxoplasma	3	0.4	2	1
IBD	3	0.4	1	2
HTLV-1-associated uveitis	2	0.3	0	2
Diabetic iridocyclitis	2	0.3	2	0
Post-streptococcal uveitis	2	0.3	2	0
Sympathetic ophthalmia	2	0.3	1	1
Syphilis	2	0.3	2	0
Geographic chorioretinopathy	1	0.1	1	0
HIV retinopathy	1	0.1	1	0
Relentless recurrent chorioretinitis	1	0.1	0	1
BDUMP	1	0.1	0	1
Neuroretinitis	1	0.1	1	0
PORN	1	0.1	0	1
Uveitis because of IPL	1	0.1	0	1
Uveitis because of nivolumab	1	0.1	1	0
Non-necrotising herpetic retinopathy	1	0.1	0	1
Uveitis because of pembrolizumab	1	0.1	0	1

Table 2 continued

	Patients (*n*)		Sex	
	n	%	Male	Female
Immune reconstruction syndrome	1	0.1	0	1
Uveitis because of MAC	1	0.1	1	0
Iridocyclitis because of cellulitis	1	0.1	0	1
PIC + AZOOR	1	0.1	1	0
Lens induced uveitis	1	0.1	0	1
Iridocyclitis because of Kawasaki disease	1	0.1	0	1
Masquerade syndrome (Choroidal metastasis of breast cancer)	1	0.1	0	1
Relentless placoid chorioretinitis	1	0.1	1	0
Classified uveitis	449	61.3	224	225
Unclassified uveitis	283	38.7	109	174

AAU acute anterior uveitis, *APMPPE* acute posterior multifocal placoid pigment epitheliopathy, *AZOOR* acute zonal occult outer retinopathy, *HIV* human immunodeficiency virus, *HLA* human leukocyte antigen, *HTLV-1* human T lymphotropic virus type-1, *IBD* inflammatory bowel disease, *IPL* idiopathic plasmacytic lymphadenopathy with polyclonal hyperimmunoglobulinemia, *MAC* Mycobacterium avium complex, *MEWDS* multiple evanescent white dot syndrome, *PIC* punctate inner choroidopathy, *BDUMP* bilateral diffuse uveal melanocytic proliferation, PORN posterior outer retinal necrosis, *RA* rheumatoid arthritis, *TINU* tubulointerstitial nephritis and uveitis

Table 3 Diagnostic methods for herpetic iritis

Diagnostic method	Patients, *n* (%)
Cytomegalovirus detection with PCR using aqueous humour	29 (59.2)
Skin lesions of herpes zoster ophthalmicus and granulomatous iridocyclitis	10 (20.4)
Herpes simplex virus detection with PCR using aqueous humour	5 (10.2)
Varicella zoster virus detection with PCR using aqueous humour	4 (8.2)
Human herpes virus-7 detection with PCR using aqueous humour	1 (2.0)

PCR polymerase chain reaction

these findings suggested that herpetic iridocyclitis is common in older individuals. Thus, we expect that the incidences of herpetic iridocyclitis and intraocular lymphoma will further increase in Japan.

Some causative diseases of uveitis tend to occur more frequently in a particular age range. For example, herpes iritis and intraocular malignant lymphoma are considered to be common in the elderly [42, 43]. To clarify these trends in our study population, we divided the patients into children to young (< 20 years), young to middle-aged (20–59 years), and elderly (≥ 60 years) individuals (Table 4). Our results revealed that the most frequent uveitis causes in patients aged ≥ 60 years were sarcoidosis, intraocular lymphoma, and herpetic iridocyclitis. The incidences of these top three diseases remain high compared to those reported in a study conducted 3 years prior [19].

We speculated that the long-term increase in the number of patients with herpetic iridocyclitis and the decrease in the number of patients with Posner-Schlossman syndrome and unclassified acute anterior uveitis may be attributed to the recurrent use of PCR assays for HSV-, VZV-, and CMV-DNA using anterior chamber fluid. Since 2012, we have performed these PCR assays routinely in cases of suspected herpetic iridocyclitis. This might lead to increases in referrals of patients with suspected herpetic iridocyclitis. Regarding the increase in the incidence of intraocular lymphoma, there are three potential reasons. First, we actively conducted diagnostic vitrectomies for patients with suspected intraocular lymphoma, which increased the rate of diagnosis. Second, there has been an increase in the number of patients with primary central nervous system lymphoma [44]; intraocular lymphoma is classified as

Table 4 Frequency of new patients with uveitis (2016–2018) by age

< 20 years (n = 35)	Patients, n (%)	20–59 years (n = 329)	Patients, n (%)	≥ 60 years (n = 368)	Patients, n (%)
Juvenile chronic iridocyclitis	11 (31.4)	Behçet's disease	32 (9.7)	Sarcoidosis	49 (13.3)
TINU	3(8.6)	Unclassified AAU	24(7.3)	Intraocular lymphoma	32 (8.7)
MEWDS	2 (5.7)	Vogt–Koyanagi–Harada disease	21 (6.4)	Herpetic iridocyclits	29 (7.9)
AZOOR complex	1 (2.9)	Herpetic iridocyclitis	20 (6.1)	Bacterial endophthalmitis	18 (4.9)
Iridocyclitis because of Kawasaki disease	1 (2.9)	Sarcoidosis	16 (4.9)	Vogt–Koyanagi–Harada disease	14 (3.8)
Post-streptococcal uveitis	1 (2.9)	Fuchs heterochromic iridocyclitis	14 (4.3)	Cytomegalovirus retinitis	9 (2.4)
Unclassified AAU	1 (2.9)	HLA-B27-associated AAU	13 (4.0)	Unclassified AAU	9 (2.4)
Unknown	15 (42.3)	Posner-Schlossman syndrome	11 (3.3)	Posner-Schlossman syndrome	8 (2.2)
		Intraocular lymphoma	8 (2.4)	Tuberculosis	6 (1.6)
		MEWDS	4 (1.2)	Fungal endophthalmitis	6 (1.6)
		Acute retinal necrosis	4 (1.2)	Acute retinal necrosis	4 (1.1)
		Tuberculosis	4 (1.2)	Fuchs heterochromic iridocyclitis	3 (0.8)
		Bacterial endophthalmitis	3 (0.9)	HLA-B27-associated AAU	3 (0.8)
		PIC	3 (0.9)	IBD	2 (0.5)
		Psoriatic uveitis	3 (0.9)	HTLV-1-associated uveitis	2 (0.5)
		Juvenile chronic iridocyclitis	3 (0.9)	Sclerouveitis because of scleroderma	2 (0.5)
		Iridocyclitis because of RA	3 (0.9)	Uveitis because of MAC	1 (0.3)
		Fungal endophthalmitis	3 (0.9)	APMPPE	1 (0.3)
		Toxoplasma	3 (0.9)	Iridocyclitis because of cellulitis	1 (0.3)
		Cytomegalovirus retinitis	3 (0.9)	Behçet's disease	1 (0.3)
		Sympathetic ophthalmia	2 (0.6)	Uveitis because of Nivolumab	1 (0.3)
		Syphilis	2 (0.6)	Neuroretinitis	1 (0.3)
		Systemic lupus erythematosus	2 (0.6)	Systemic lupus erythematosus	1 (0.3)
		AZOOR	2 (0.6)	Psoriatic uveitis	1 (0.3)
		APMPPE	2 (0.6)	Bilateral diffuse uveal Melanocytic proliferation (BDUMP)	1 (0.3)
		Diabetic iritis	2 (0.6)	PORN	1 (0.3)
		Immune reconstruction syndrome	1 (0.3)	Iridocyclitis because of RA	1 (0.3)
		IBD	1 (0.3)	Non-necrotising herpetic retinopathy	1 (0.3)
		Masquerade syndrome (Choroidal metastasis of breast cancer)	1 (0.3)	Uveitis because of Pembrolizumab	1 (0.3)
		Post-streptococcal uveitis	1 (0.3)	Lens-induced uveitis	1 (0.3)
		Relentless recurrent chorioretinitis	1 (0.3)	Unknown	158 (42.9)
		PIC + AZOOR	1 (0.3)		
		Sclerouveitis because of scleroderma	1 (0.3)		
		Geographic chorioretinopathy	1 (0.3)		
		Uveitis because of IPL	1 (0.3)		
		TINU	1 (0.3)		

Table 4 continued

< 20 years (n = 35)	Patients, n (%)	20–59 years (n = 329)	Patients, n (%)	≥ 60 years (n = 368)	Patients, n (%)
		HIV retinopathy	1 (0.3)		
		Unknown	110 (33.4)		
Total	35	Total	329	Total	368

AAU acute anterior uveitis, *APMPPE* acute posterior multifocal placoid pigment epitheliopathy, *AZOOR* acute zonal occult outer retinopathy, *HIV* human immunodeficiency virus, *HLA* human leukocyte antigen, *HTLV-1* human T lymphotropic virus type-1, *IBD* inflammatory bowel disease, *IPL* idiopathic plasmacytic lymphadenopathy with polyclonal hyperimmunoglobulinemia, *MAC* Mycobacterium avium complex, *MEWDS* multiple evanescent white dot syndrome, *PIC* punctate inner choroidopathy, *PORN* posterior outer retinal necrosis, *RA* rheumatoid arthritis, *TINU* tubulointerstitial nephritis and uveitis

Table 5 Shifts in the distribution of the anatomic localisation of uveitis (2004–2018)

	Period				
	2004–2006[a]	2007–2009[a]	2010–2012[b]	2013–2015[b]	2016–2018[b]
New patients (n)	377	468	643	750	732
Anatomic localisation, n (% of new patients)					
Anterior uveitis	184 (48.8)	225 (48.0)	322 (50.1)	289 (38.5)	242 (33.1)
Intermediate uveitis	-[a]	-[a]	10 (1.6)	12 (1.6)	11 (1.5)
Posterior uveitis	36 (9.6)	73 (15.6)	86 (13.4)	94 (12.5)	52 (7.1)
Panuveitis	157 (41.6)	170 (36.3)	225 (35.0)	355 (47.3)	427 (58.3)

Data of patients from years 2004–2018 [17–19]

[a]The classification of the International Ocular Inflammation Society was adopted. Intermediate uveitis included in the definition of posterior uveitis [27]

[b]The classification of the Standardization of Uveitis Nomenclature was adopted [15]

Table 6 Shifts in the numbers of new patients with uveitis according to age (2004–2018)

	Period				
	2004–2006	2007–2009	2010–2012	2013–2015	2016–2018
New patients (n)	426	535	695	750	732
Age (years)	53.2 ± 17.7	51.6 ± 17.8	53.6 ± 18.6	56.5 ± 18.5	56.4 ± 19.0
Age range, years, n (% of new patients)					
< 20	11 (2.6)	26 (4.9)	29 (4.2)	31 (3.9)	35 (4.8)
20–59	251 (58.9)	308 (57.6)	354 (50.9)	358 (44.8)	329 (44.9)
≥ 60	164 (38.5)	201 (37.6)	312 (44.9)	409 (51.1)	368 (50.3)

Data of patients from years 2004–2018 [17–19]

central nervous system lymphoma, and we predict that a greater increase in the number of patients with central nervous lymphoma will correspond to a greater increase in the number of patients with intraocular lymphoma. Third, as one-arm prospective clinical trials for primary intraocular lymphoma that aim to suppress brain seeding have been carried out since 2008 [34], referrals of patients with suspected intraocular lymphoma might be increasing in our hospital.

The percentage of patients aged < 20 years increased from 2004 to 2018 (2.4%, 4.1%, 4.2%, 4.1%, and 4.8% in 2004–2006, 2007–2009, 2010–2012, 2013–2015, and 2016–2018, respectively). This may have contributed to the increase of patients with JCI. The actual reasons for increasing incidence of childhood uveitis in our hospital remain unknown, but we speculate that the chances of referral to our facility for highly specialised pediatric uveitis may have increased. In addition, among the JCI patients, there were no patients with juvenile idiopathic arthritis, in line with previous reports from Japan [45].

In contrast, the incidences of sarcoidosis, Behçet's disease, and VKH gradually decreased at our institution. We cannot provide adequate reasons as to why the frequencies of these diseases decreased, but it might be attributed to the fact that the severity of Behçet's uveitis is milder in Japan and can be treated without referrals [46].

This study had several limitations. First, it was a retrospective study conducted in a tertiary referral university hospital. Most of the patients were referred to our hospital. Thus, there may be a selection bias towards patients with severe disease. Second, the study period was only 3 years. However, the data of > 700 patients were analysed in this study, and thus, we believe that the results of this study are reflective of the current patterns of uveitis in Japan. Further multicentre studies comparing different regions of Japan would be beneficial for characterising recent trends of uveitis in Japan.

Conclusions

The recent patterns of uveitis in the central Tokyo area have indicated increasing incidences of herpetic iridocyclitis, bacterial endophthalmitis, intraocular lymphoma, and juvenile chronic iridocyclitis. This trend may be associated with the recent advances in the examination tools used for the diagnosis of uveitis, particularly PCR, the change in population of the referred patients, such as increase in number of children presenting with uveitis, and the aging Japanese population. As the incidences of these diseases are increasing in Japan, ophthalmologists should focus on these diseases and perform tests, such as PCR and vitreous biopsy, for definitive diagnoses without delay.

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Authors' contributions TS was involved in the study design, data collection, analysis of the results, and drafting of the manuscript. TK and SS participated in the study design, data collection, and reviewing and editing of the manuscript. RT, KK, HN, MT, HK, and MA participated in the data collection and reviewing and editing of the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials The datasets used and analysed in the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Compliance with ethical standards

Conflict of interests The authors declare that they have no competing interests.

Ethical approval This retrospective study was approved by the research ethics committee of the Graduate School of Medicine and Faculty of Medicine at The University of Tokyo. This study was conducted in compliance with the Declaration of Helsinki and the ethical guidelines for medical and health research involving human subjects.

Consent to participate We used an opt-out approach, which is a substitute for consent, by informing participants of the purpose and conduct of the study and guaranteeing them the opportunity to be excluded, rather than obtaining direct consent from each patient.

Consent for publication Not applicable.

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