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Original Article

Follow-up Findings of Non-infectious Pediatric Uveitis Patients

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Abstract

Objectives: In this study, we aimed to describe the demographic and clinical findings of children with uveitis at a tertiary pediatric rheumatology and ophthalmology center.

Materials and Methods: A retrospective cross-sectional study was conducted with 46 patients who were diagnosed with uveitis before the age of 16 years and were followed regularly for at least 6 months between January 2013 and June 2019. Demographic data, uveitis characteristics, underlying diseases, systemic treatment modalities, drug side effects, complications, and surgical intervention were evaluated.

Results: Eighty-three eyes of 46 patients were included in the study. The mean age at diagnosis of uveitis was 9.2±4.5 (1.6-15.6) years, and the mean uveitis follow-up period was 54±41 (6-191) months. Twenty-one patients (45.7%) had uveitis associated with rheumatologic diseases. Juvenile idiopathic arthritis was the most common disease (23.9%). Visual acuity was categorized as moderately impaired in 6 eyes (7.2%), severely impaired in 4 eyes (4.8%), and blindness in 1 eye (1.2%). Methotrexate (87%) was the most frequently used systemic immunosuppressive agent in treatment. Adalimumab (73.9%) was added to treatment in resistant cases. Thirty-five patients (76.1%) had complications in at least 1 eye secondary to uveitis or uveitis treatment. Posterior synechiae (11 eyes, 13.2%) was the most common complication during treatment.

Conclusion: In order to preserve visual acuity, pediatric uveitis should be recognized early and especially persistent/chronic cases should be started on effective systemic treatment immediately.

Keywords: Uveitis, immunosuppressive therapy, adalimumab, tocilizumab, complication

Introduction

Uveitis basically refers to an inflammatory condition of the highly vascularized and pigmented uveal layer of the eye, although the vitreous, retina, and retinal vascular structures can also be affected by the inflammatory process due to their close anatomical proximity. In a broad sense, the term uveitis suggests intraocular inflammation.

Pediatric uveitis, which accounts for approximately 10-15% of uveitis series, poses unique challenges in terms of diagnosis, follow-up, and treatment.[1,2,3] The insidious nature of uveitis in childhood and pediatric patients' inability to express their

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complaints adequately and cooperate with eye examination can delay the diagnosis. More importantly, pediatric uveitis tends to be more severe and become chronic. All of these factors increase the frequency of complications that can lead to vision loss.[3,4] Therefore, patients with refractory uveitis require pediatric rheumatology follow-up both to initiate systemic treatment and detect underlying rheumatologic disease.

In this study, we evaluated the demographic data, uveitis characteristics, underlying rheumatologic diseases, treatment modalities, complications during follow-up, and adverse drug effects in uveitis patients being followed in the ophthalmology and pediatric rheumatology departments.

Materials and Methods

After obtaining approval from the Pamukkale University Ethics Committee for this retrospective cross-sectional study, we reviewed the records of 57 uveitis patients who were diagnosed with non-infectious uveitis in the ophthalmology department and were referred to the pediatric rheumatology department for etiological studies and systemic therapy between January 2013 and June 2019. Inclusion criteria were being diagnosed with uveitis before the age of 16 years, being followed up for at least 6 months, attending follow-up visits regularly, and having no missing data. Forty-six patients who met these criteria were included in the study.

The patients' demographic data, uveitis characteristics, underlying diseases, systemic treatment modalities, adverse drug effects, uveitis complications, and surgical history were evaluated. Most recent best corrected visual acuities assessed by Snellen chart were noted. Intraocular pressure and anterior and posterior examination findings were recorded. Level of vision was classified according to World Health Organization criteria.[5] Best corrected visual acuity of 3/60 or worse in the better-seeing eye was considered blindness; between 3/60 and ≤6/60 was severe impairment, and between 6/60 and ≤6/18 was moderate impairment.[6]

Uveitis was categorized according to the criteria specified by the International Uveitis Working Group. Patients were grouped according to these criteria as anterior uveitis (primary site of inflammation is anterior chamber; presence of iritis, iridocyclitis, and anterior cyclitis), intermediate uveitis (primary site of inflammation is vitreous; presence of pars planitis, posterior cyclitis, hyalitis), posterior uveitis (primary site of inflammation is retina/choroid; presence of choroiditis, chorioretinitis, retinitis, neuroretinitis), and panuveitis (involvement of all regions).[7]

The patients' uveitis was classified according to anatomic location (anterior, intermediate, posterior, panuveitis), affected eye (right, left, bilateral), and etiology.

Follow-up frequencies are determined in our center as specified in the guidelines. The follow-up interval was 2-3 months for patients with stable uveitis, less than 3-4 weeks while tapering topical steroids, and less than 2 months while tapering systemic therapy.[8]

Controlled uveitis was defined as inactive uveitis or the presence of up to grade 1+ anterior chamber cells provided that there were no new complications secondary to inflammation. The presence of grade 1+ or more anterior chamber cells or the appearance of new signs/complications of inflammation was regarded as loss of control of uveitis.[7,8]

Juvenile idiopathic arthritis (JIA) was diagnosed based on the International League of Associations for Rheumatology diagnostic criteria; Behçet's disease was diagnosed according to the pediatric Behçet diagnostic criteria published in 2015; the diagnosis of tubulointerstitial nephritis and uveitis (TINU) was made by demonstrating renal pathology on biopsy; and the diagnosis of sarcoidosis was made clinically.[9,10]

Results

A total of 83 eyes of 46 patients were included in the study. The patients' demographic characteristics, unilateral/bilateral involvement rates, uveitis locations, and complication and surgical intervention rates are summarized in Table 1. The mean age at uveitis diagnosis was 9.2±4.5 years (median: 8.3, range: 1.6-15.6) and the mean duration of uveitis follow-up was 54±41 months (median: 49, range: 6-191).

Uveitis was associated with rheumatologic disease in 21 patients (45.7%) and was idiopathic in 25 patients (54.3%) (Table 2). JIA was the most common systemic disease (23.9%) and only caused anterior uveitis (11 patients). JIA was oligoarticular in 8 patients, polyarticular in 2 patients, and enthesitis-related in 1 patient. Uveitis was diagnosed after the diagnosis of JIA in 8 patients, simultaneously in 2 patients, and before the onset of joint findings in 1 patient.

Two patients had suspected sarcoidosis initially presenting as isolated uveitis with no systemic organ involvement and the other two patients had inherited sarcoidosis (Blau syndrome) and early-onset adult sarcoidosis. Of the 4 patients followed for Behçet uveitis, all had oral aphthae, 2 had genital aphthae, and 1 had skin and vascular involvement. Both patients with TINU developed anterior uveitis while being followed for creatinine elevation.

Best corrected visual acuity was 0.29±0.59 LogMAR (median: 0.1, range: 0-3) at the first visit and 0.15±0.30 LogMAR (median: 1, range: 0-1.3) at the last visit (p=0.04, Wilcoxon). Visual acuity was categorized as moderately impaired in 6 eyes (7.2%), severely impaired in 4 eyes (4.8%), and blindness in 1 eye (1.2%). The mean number of attacks was 3.6±2.3 (median: 3, range: 1-9).

Local uveitis treatment was effective in only 2 patients (4.3%) patients; the 44 patients (95.7%) whose disease could not be controlled with local treatment were given short-term systemic steroid at 1-2 mg/kg/day (maximum 60 mg/day), and 10 patients (21.7%) received a periocular steroid injection. Of 44 patients (95.7%) with complicated uveitis at diagnosis (n=7), systemic corticosteroid-resistant uveitis (n=27), or additional systemic disease (n=10), 40 patients (87%) were started on methotrexate 15 mg/m^2/week (subcutaneous, maximum 25 mg/

dose) and 4 (8.4%) were started on azathioprine 1-2 mg/kg/day (oral, maximum 150 mg/day). Twenty-five of the patients treated with methotrexate had anterior uveitis, 10 had intermediate uveitis, 2 had posterior uveitis, and 3 had panuveitis. Of the patients treated with azathioprine, 2 had anterior uveitis and 2 had panuveitis (Table 3). The mean duration of methotrexate use, the most preferred systemic immunosuppressive agent, was 42.40±41.68 months (median: 28.50, range: 3-190).

Uveitis could not be controlled in 34 patients (73.9%) under systemic immunosuppressive therapy. Most cases of uveitis that did not respond to immunosuppressive therapy were idiopathic and anterior uveitis (Table 4). An anti-TNF agent (adalimumab) was added to treatment for these patients (Table 3). Adalimumab was administered at 24 mg/m^2 every 2 weeks (subcutaneous, maximum 40 mg/dose) for a mean duration of 31.50±21.39 months (median: 27, range: 6-84). In 10 patients (21.7%) whose uveitis attacks continued while receiving adalimumab, the treatment frequency was increased and injections of the same dose were given weekly. In 6 patients, attacks were controlled after a mean of 11.67±5.28 months (median: 12, range: 6-20), after which treatment was continued at the normal injection interval (every 2 weeks). One patient with refractory macular edema despite a year of adalimumab therapy was started on an interleukin-6 antagonist (tocilizumab) at 8 mg/kg/2 weeks (intravenous infusion, maximum 400 mg/dose) as an alternative treatment.

Table 1. The patients' demographic and clinical characteristics

Sex	Female	20 (43.5%)
	Male	26 (56.5%)
Ocular involvement	Unilateral	9 (19.6%)
	Bilateral	37 (80.4%)
Uveitis location	Anterior	27 (58.7%)
	Intermediate	12 (26.1%)
	Posterior	2 (4.3%)
	Panuveitis	5 (10.9%)
Complication	Yes	35 (76.1%)
	No	11 (23.9%)
Surgical intervention	Yes	13 (28.3%)
	No	33 (71.7%)

Five patients with controlled uveitis are being followed without medication. Medication-free follow-up was possible after local treatment and short-term systemic steroid therapy in 2 patients, after 12 months of methotrexate therapy in 2 patients, and after 108 months of methotrexate and 54 months of adalimumab therapy in 1 patient. The other patients with controlled uveitis were followed up with treatment as follows: As 2 patients using adalimumab and methotrexate had no attacks for 24 months of adalimumab therapy, adalimumab was discontinued and methotrexate therapy was continued. The frequency of adalimumab was increased to 3 weeks in both patients. During the treatment discontinuation phase, first adalimumab and then methotrexate were discontinued. In the first stage, treatment intervals were extended and then the doses were reduced. All uveitis patients who reached the treatment discontinuation stage were in the idiopathic uveitis category.

Extraocular complications that occurred during systemic treatment included intolerance (methotrexate, n=6, 13%) and liver toxicity (azathioprine, n=1, 2.2%). Three patients using biological agents were treated with isoniazid for 9 months due to positive screening test (without any signs of disease).

Complications secondary to uveitis or uveitis treatment were detected in at least one eye of a total of 35 patients (76.1%), including at the time of diagnosis in 7 patients. These complications were glaucoma, cataract, posterior synechiae, band keratopathy, macular edema, and retinal detachment (Figure 1). The most common complication that developed during treatment was posterior synechia (n=11). As a result of complications, 2 patients (4.3%) underwent cataract surgery, 3 patients (6.5%) underwent glaucoma surgery, and 2 patients (4.3%) underwent both cataract and glaucoma surgery.

Discussion

In this study we examined our experience with non-infectious pediatric uveitis. Almost half (45.7%) of our uveitis patients had an underlying rheumatologic disease, and nearly all of them required the addition of systemic steroids and immunosuppressants. Moderate vision loss was present in 7.2%, severe vision loss in 4.8%, and blindness in 1.2% of the patients in our study.

Table 2. Distribution of uveitis location and complications according to underlying disease

		Diagnosis					Total
		Idiopathic	**JIA**	**Sarcoidosis**	**TINU**	**BD**	
Uveitis location	Anterior	11 (23.9%)	11 (23.9%)	3 (6.5%)	2 (4.3%)	0	27 (58.7%)
	Intermediate	11 (23.9%)	0	0	0	1 (2.2%)	12 (26.1%)
	Posterior	1 (2.2%)	0	0	0	1 (2.2%)	2 (4.3%)
	Panuveitis	2 (4.3%)	0	1 (2.2%)	0	2 (4.3%)	5 (10.9%)
Complication	Yes	21 (45.6%)	7 (15.2%)	3 (6.5%)	1 (2.2%)	3 (6.5%)	35 (76.1%)
	No	4 (8.7%)	4 (8.7%)	1 (2.2%)	1 (2.2%)	1 (2.2%)	11 (23.9%)
Total		25 (54.3%)	11 (23.9%)	4 (8.7%)	2 (4.3%)	4 (8.7%)	46 (100%)

JIA: Juvenile idiopathic arthritis, TINU: Tubulointerstitial nephritis and uveitis, BD: Behçet's disease

Pediatric uveitis is reported at a frequency of 10-15% in case series and is often idiopathic, bilateral, and manifests as anterior uveitis.[1,2,3] In our patient group, 80.4% of cases were bilateral, 54.3% were idiopathic, and 58.7% of patients had anterior uveitis.

Although uveitis is reported slightly more frequently in females than males, the female to male ratio among our patients was 1:1.3 (20 girls, 26 boys).[4,11,12] Similarly, a recent publication from Turkey reported this ratio to be 1:1.1 in non-infectious pediatric uveitis.[13]

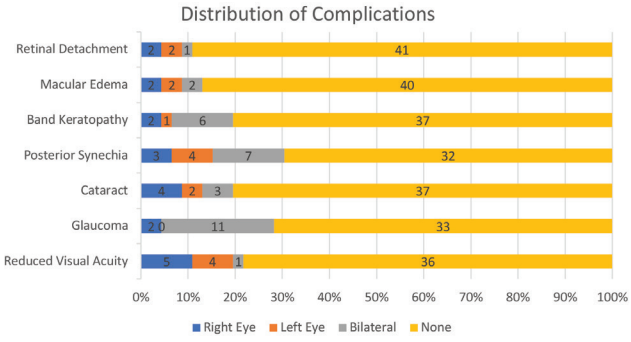

Figure 1. Complication rates

In a review of pediatric uveitis, Tugal-Tutkun[3] stated that uveitis series from North America and Europe showed rates of 35-50% for anterior uveitis, 10-20% for intermediate uveitis, 15-25% for posterior uveitis, and 10-20% for panuveitis. The prevalence of anterior uveitis has been reported to be 46-62% in recent publications.[4,11,12] In our series, the rate of anterior uveitis was 58.7%, close to the upper limit of the range specified in current reports. Anterior uveitis was idiopathic in 23.9% of cases and associated with the underlying pathologies of JIA in 23.9%, sarcoidosis in 6.5%, and TINU in 4.3% of patients. In another recent publication from our country, the two most common etiologies of pediatric uveitis were idiopathic in 47.8% and JIA in 36.9% of patients.[14] A retrospective study in Finland reported an anterior uveitis rate of 93%, which was attributed to JIA in 61% of patients.[15] Our cases of intermediate uveitis (26.1%) were predominantly pars planitis (23.9%). Intermediate uveitis was reported to be the most frequent form (34.2%) in another study from Turkey but was not detected in any patients in a Japanese study, while non-infectious intermediate uveitis was observed at rates of 25.6% and 19.9% in studies conducted in Brazil and the USA, respectively.[4,11,12,13] Posterior uveitis (4.3%) and panuveitis (10.9%) were less common in our study.

Anterior uveitis was present in 100% of patients with JIA and TINU and 75% of patients with sarcoidosis, whereas

Table 3. Distribution of immunosuppressive therapies by indication

Immunosuppressive therapy	Primary systemic disease	Uveitis				Total
		Anterior uveitis	Intermediate uveitis	Posterior uveitis	Panuveitis	
Methotrexate	10	17	7	2	4	40
Azathioprine	0	3	1	0	0	4
Adalimumab	1	20	6	2	5	34
Infliximab	0	1	0	0	0	1
Tocilizumab	0	0	0	1	0	1

Table 4. Distribution of uveitis refractory to immunosuppressive therapy according to underlying disease and uveitis location

		Treatment non-response	Treatment response	Total
Underlying disease	Idiopathic	18 (39.1%)	7 (15.2%)	25 (54.3%)
	JIA	10 (21.7%)	1 (2.2%)	11(23.9%)
	Sarcoidosis	4 (8.7%)	0	4 (8.7%)
	TINU	0	2 (4.3%)	2 (4.3%)
	BD	2 (4.3%)	2 (4.3%)	4 (8.7%)
	Total	34 (73.9%)	12 (26.1%)	46 (100%)
Uveitis location	Anterior	21 (45.7%)	6 (13%)	27 (58.7%)
	Intermediate	8 (17.4%)	4 (8.7%)	12 (26.1%)
	Posterior	2 (4.3%)	0	2 (4.3%)
	Pan	3 (6.5%)	2 (4.3%)	5 (10.9%)
	Total	34 (73.9%)	12 (26.1%)	46 (100%)

JIA: Juvenile idiopathic arthritis, TINU: Tubulointerstitial nephritis and uveitis, BD: Behçet's disease

isolated anterior uveitis was not seen in any Behçet's patients. Involvement rates in Behçet's disease were 25% intermediate, 25% posterior, and 50% panuveitis.

In this series, which had a final visual acuity of 0.15±0.30 LogMAR, the prevalence of legal blindness (3/60 or worse) was determined to be 1.21%. In pediatric uveitis studies conducted in Turkey, Yüce et al.[16] reported a visual acuity of 20/200 or worse in 4 eyes and 20/40 or worse in 18 of 64 eyes with pediatric uveitis, and Yalçındağ et al.[13] reported a visual acuity of 20/200 or worse in 8 eyes and between 20/200 and 20/40 in 16 eyes. Recent studies have indicated that the rate of legal blindness among uveitis patients has decreased from 19-69.6% to 7.7-9.7%.[4,12,17,18,19] In a French pediatric uveitis series, there were no legally blind patients but 9 (6%) had monocular blindness.[20] This improvement is believed to be related to the increasing use of biological agents in the treatment of uveitis over the last decade.

Complications are common in pediatric uveitis due to its tendency for chronification and recurrence. The frequency of one or more complications in recent pediatric uveitis series is reported as approximately 70%.[4,12] Complications occur secondary to treatment in addition to the primary disease. In recent series, the most common complications were cataract (44-52%), followed by secondary glaucoma (23-33%), band keratopathy (13-37%), and posterior synechia (19-54%).[4,12] Gautam Seth et al.[21] reported complication rates of 24% for cataract, 18.29% for band keratopathy, and 6.29% for glaucoma in their series. In our study, 76.1% of our patients developed at least one complication, with synechia (30.4%) and glaucoma (28.3%) being the most common. Seven patients (19%) whose cataract and glaucoma could not be controlled with medical therapies were treated surgically. Two patients underwent cataract surgery, 3 underwent glaucoma surgery, and 2 patients underwent combined cataract and glaucoma surgery. Yalçındağ et al.[13] reported a complication rate of 26.1% and surgical treatment rate of 2.8% in their series, while Ferrara et al.[12] reported that the surgical treatment rate was 8-46% in the literature and 38% in their series. In a recent study from Turkey, 34% of patients had complications, the most common of which was posterior synechia (18.6%), and 8 eyes (5.1%) underwent surgical treatment due to complications.[14]

In treatment management, the presence of complications and systemic disease accelerates the transition from local treatment to systemic treatment. The general tendency in systemic treatment is to use systemic steroids as first-line therapy. Depending on the threat to vision and the underlying systemic disease, the first treatment may be an anti-TNF agent. However, in cases of nonresponse, steroid dependence, or the need for long-term treatment for systemic disease, a second immunosuppressive therapy should be added to enable discontinuation of the steroid within a reasonable time due to its adverse effects.[3,22] Methotrexate is usually the first choice of immunosuppressive, as it is both safe and effective in patients with pediatric uveitis.[22,23] In our study, 44 patients (95.7%) who did not respond to local treatments were given short-term systemic steroid therapy. Forty patients (87%) needed additional methotrexate and 4 patients (8.7%) patients needed azathioprine. However, treatment was discontinued in 6 patients (13%) who could not tolerate methotrexate and 1 patient (2.2%) receiving azathioprine due to liver toxicity. Treatment was continued with a biologic agent. In contrast, uveitis could only be controlled with methotrexate in 7 patients (15.2%) and with azathioprine in 1 patient (2.2%).

Adalimumab was initiated in 34 patients (73.9%) whose uveitis did not respond to immunosuppressive therapy. Of these, 1 patient who required emergency surgery was given infliximab followed by adalimumab. Three JIA patients using etanercept due to severe joint involvement were switched to adalimumab when they developed uveitis. Biologic agents are revolutionary in the treatment of refractory ocular inflammation that cannot be controlled with disease-modifying agents. Infliximab and adalimumab are highly effective in the treatment of refractory pediatric uveitis.[24] Although adalimumab therapy has the advantage of being safer and easier use in pediatric patients, infliximab provides satisfactory results in cases where a rapid effect is desired and emergency surgery is required.[25] In our series, the adalimumab treatment interval was reduced from 2 weeks to 1 week in 10 patients (21.7%) whose attacks were not adequately controlled despite all of these treatments. Although there are very few examples in the literature of weekly adalimumab therapy in refractory uveitis, our patients benefited from this approach.[26,27] In 6 patients whose uveitis could be controlled, the treatment frequency was returned to normal and treatment was discontinued in 1 patient during follow-up. The response time to weekly adalimumab was quite heterogeneous, with a mean of 11.67±5.28 months (range: 6-20). While 3 patients continued weekly treatment, 1 patient was switched to tocilizumab because of persistent macular edema despite weekly treatment. This patient's symptoms were controlled and macular edema regressed after 4 months of tocilizumab therapy. Favorable outcomes in adult uveitis have suggested that tocilizumab may also be used in refractory pediatric cases. In addition, the use of abatacept, rituximab, and tocilizumab for anti-TNF-refractory uveitis is included in the 2018 uveitis treatment recommendations of the SHARE group.[28] Pediatric patients with underlying rheumatologic disease or who are nonresponsive to local therapies and need systemic immunosuppressants should be followed up in collaboration with a rheumatologist.

Caution in terms of infection is recommended when administering biologic agents that have been recently introduced and have even more limited pediatric use. Screening for diseases such as tuberculosis, hepatitis B, and hepatitis C is necessary before initiating anti-TNF therapy.[29] Annual follow-up for hepatitis B and tuberculosis is recommended. TNF inhibitors increase the risk of tuberculosis infection and reactivation.[30] During our follow-up, 3 patients with large indurations on purified protein derivative test were given prophylaxis to prevent reactivation. In addition to these, no latent or opportunistic infections were encountered.

Study Limitations

A limitation of our study is that it was designed as a retrospective, single-center study. In addition, our uveitis series did not include any patients who responded rapidly to local therapies and thus did not require systemic treatment. Especially in young children, it may not be possible to perform examinations used to detect subclinical posterior segment findings due to the lack of cooperation, which may cause misclassification in terms of anatomic location.

Conclusion

As pediatric uveitis can cause vision loss if not treated appropriately, early recognition, initiation of effective systemic treatment in refractory and chronic cases, and close follow-up for complications are essential. In cases where uveitis cannot be controlled even with standard immunosuppressive therapy and biologic agents, increasing the dosing frequency of anti-TNF may have therapeutic benefit. For patients with systemic diseases that can lead to the development of uveitis, pediatric rheumatologists should inform the families about uveitis and its symptoms and refer them to regular eye examinations for uveitis screening.

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Ethics

Ethics Committee Approval: Pamukkale University Non-Invasive Clinical Research Ethics Committee approval number: 60116787-020/75663.

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Authorship Contributions

Surgical and Medical Practices: Z.E.T., G.O.Y., S.A., E.N.Ç., S.Y., Concept: Z.E.T., E.N.Ç., S.Y., Design: Z.E.T., E.N.Ç., S.Y., Data Collection or Processing: Z.E.T., G.O.Y., S.A., Analysis or Interpretation: Z.E.T., E.N.Ç, S.Y., Literature Search: Z.E.T., Writing: Z.E.T.

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