



Outcome of Pediatric Uveitis at an University Clinic

Bir Üniversite Kliniğindeki Pediatrik Üveit Olgularının Sonuçları

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Summary

Purpose: To determine the etiology, clinical course, complications, and outcome of uveitis in pediatric patients.

Material and Method: We retrospectively reviewed the medical charts of 64 eyes of 43 patients, who had been followed up at a University clinic. Demographic and etiological features, clinical course, complications, and visual outcome were analyzed.

Results: Male/female ratio was 22/21. Median age at the first visit was 14 (3-18) years. Unilateral involvement was observed in 22 (51.16%) patients. Anterior uveitis was the most common form (67.19%). Idiopathic uveitis was seen in 25 (58.14%) patients. The most commonly identified etiological entities were juvenile idiopathic arthritis (JIA) (5 patients) and Behcet's disease (4 patients). Both glaucoma and cataract were the most common complications (12.50%, 6.25%; respectively). Final VA was equal or better than 20/40 in 47 eyes (73.43%).

Discussion: Uveitis in pediatric patients was mostly idiopathic. The most commonly identified etiologic entities were JIA and Behcet's disease. Final visual outcome was favorable with appropriate treatment. (*Turk J Ophthalmol* 2013; 43: 395-401)

Key Words: Behcet's disease, juvenile idiopathic arthritis, complications, pediatric uveitis; visual outcome

Özet

Amaç: Pediatrik hastalarda üveitin etiyolojisi, klinik seyir, komplikasyon ve sonuçlarını incelemek.

Gereç ve Yöntem: Üniversitemizde takip edilmiş olan 43 hastanın 64 gözüne ait dosya kayıtları retrospektif olarak incelendi. Demografik ve etiyolojik özellikler, klinik seyir, komplikasyonlar ve görsel sonuçlar analiz edildi.

Sonuçlar: Çalışmamızda erkek/kız oranı 22/21 idi. İlk başvuru sırasında hastaların ortanca yaş değeri 14 (3-18) yıl olarak hesaplandı. Hastaların 22 (%51,16)'sinde unilateral tutulum ile karşılaşıldı. Anterior üveit en sık görülen lokalizasyondu (%67,19). Hastalarımızın 25 (%58,14)'inde idiyopatik üveit görüldü. En sık tanımlanan etiyolojik sebep ise Juvenil İdiyopatik Artrit (JIA) (5 hasta) ve Behçet Hastalığı (4 hasta) idi. En sık karşılaşılan komplikasyonların glokom ve katarakt olduğu görüldü (sırasıyla %12,50, %6,25). Sonuç görme keskinliği 47 (%73,43) gözde 20/40 ve üzerinde idi.

Tartışma: Pediatrik hastalardaki üveit olguları çoğunlukla idiyopattır. Tanımlanabilen etiyolojik sebeplerden en sık görülenleri JIA ve Behçet Hastalığı'dır. Uygun tedavi ile sonuç görme keskinliği tatminkar olabilmektedir. (*Turk J Ophthalmol* 2013; 43: 395-401)

Anahtar Kelimeler: Behçet hastalığı, görsel sonuç, juvenil idiyopatik artrit, komplikasyon, pediatrik üveit

Introduction

Uveitis is an inflammatory disease, the frequency and etiology of which vary by geographic location depending upon host and environmental factors.¹ Children are affected by uveitis much less often than adults and account for only 5%-10% of the patients with uveitis seen in referral uveitis units.^{2,3} Despite

low incidence of uveitis, children are more susceptible to complications and worse visual prognosis than adults.⁴ The diagnosis and treatment of uveitis requires special attention in children. Relatively few symptoms or inadequate reflection of these symptoms especially by preverbal children often lead to late presentation to an ophthalmologist. Idiopathic form of uveitis is the most common figure in all age groups.^{2,5-7} Systemic diseases

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that may be associated with uveitis in children include juvenile idiopathic arthritis (JIA), Behcet's disease, sarcoidosis, tubulointerstitial nephritis, and Kawasaki disease.^{2,8}

In this study, we determined the etiology, clinical course, complications, and outcome of pediatric uveitis seen over a fifteen-year period at the Uveitis section of a University hospital.

Materials and Methods

We retrospectively reviewed the medical charts of 64 eyes of 43 patients, who had been followed up at least 6 months in our Uveitis Unit. Patients who had been diagnosed with uveitis at or before 18 years of age were included in this study. Data accumulation for the purpose of this study has been approved by the Institutional Review Board. Etiological and demographic features, clinical course and characteristics, complications and visual outcomes were noted. Patients underwent a standard clinical examination, including measurement of visual acuity (VA), slit-lamp biomicroscopy, intraocular pressure measurement, and fundus examination through a dilated pupil. Intraocular pressure measurements were done by Goldmann applanation tonometer in all cooperative children.

A detailed clinical history was taken to clarify the systemic clinical symptoms that may accompany uveitis in each patient. Appropriate laboratory tests including complete blood cell count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), antistreptolysin O (ASO), human leukocyte antigen (HLA) subtypes, autoimmune antibodies, viral serology (herpes simplex and hepatitis B viruses), bacteriological serology (*Mycobacterium tuberculosis*), parasitic serology (toxoplasma, toxocara, and syphilis serology), radiological analysis (chest X-ray; chest CT) and consultations with specialists of rheumatology, pediatrics, neurology, ear-nose-throat, gynecology, urology, thorax disease, and dentist were done in all patients who matched these analyses clinically.

Patients were categorized as: having anterior uveitis if the inflammation was primarily located in the anterior segment; having intermediate uveitis if the vitreous body was primarily involved or the inflammation involved both the anterior segment and the vitreous body or pars planitis with characteristic pars plana exudation; having posterior uveitis if retinochoroidal lesions predominated; or having panuveitis if the inflammation involved all the compartments of the eye.⁹

Records about age at diagnosis, gender, anatomic location of the involvement, laterality of disease, accompanying ocular and systemic diseases, follow-up duration, VA at first and last visit, frequency of recurrences, type of ocular complications related to uveitis, type of medical treatment and surgical interventions to correct complications of uveitis were analyzed.

Treatment for anterior uveitis consisted of topical steroids (1.0% prednisolone acetate) 2-12 times per day and cycloplegics (cyclopentolate 1%) 1-3 times per day. Systemic steroids were added to patients with anterior uveitis who experienced more than 3 attacks in a year or unresponsive to topical treatment. Patients with posterior or panuveitis were treated with systemic

steroids (prednisone 1 mg/kg/day) in addition to topical steroid treatment. Intermediate uveitis cases with cystoid macular edema or VA decrease were treated with systemic steroids. The systemic and topical dosage was reduced gradually according to the clinical control and response to the treatment. We added immunosuppressive agents such as cyclosporine (2.5 mg/kg/day), azathioprine (2 mg/kg/day) methotrexate (10-15 mg/m²/week) when systemic steroids were inadequate to control the ocular inflammation. All patients with Behcet's disease were treated with cyclosporine primarily, and all with JIA with methotrexate. In cases unresponsive to these treatments, azathioprine was preferred as the second agent. In parasitic uveitis, antihelminthic agents (trimethoprim/sulfamethoxazole 2*400/80 mg combined with, 48 hours after antihelminthic treatment, 1 mg/kg/day methylprednisolone) were added to the treatment for 6 weeks.

Statistical analysis was performed with SPSS for Windows version 12.0 program (SPSS Inc. Chicago, IL). All data, except age at first visit (median), were reported as mean±standard deviation (SD). We used Spearman's correlation analysis, Mann-Whitney U, independent t and Fisher's exact tests for statistical analysis.

Results

Our study included 64 eyes of 43 patients (male:female ratio was 22:21), with a median age of 14 (3-18) years at first visit. Pediatric uveitis cases accounted for approximately 2.14% of 2009 patients with uveitis in our Uveitis Unit. We achieved the follow-up data for a mean of 31±35 (6-180) months after the diagnosis of uveitis. Twenty one (48.84%) of the 43 patients presented with bilateral involvement and 22 (51.16%) presented with unilateral uveitis at the first visit. The intraocular inflammation was associated with an infectious agent in 5 (11.63%) of the 43 cases. Twenty-five patients (58.14%) had idiopathic whilst 18 (41.86%) had a systemic disease that could be related to. The most commonly identified entities related to uveitis were juvenile idiopathic arthritis (JIA) (5 patients; 11.63%), Behcet's disease (4 patients; 9.30%), herpes simplex virus (HSV) infection (2 patients; 4.65%), toxoplasmosis infestation (1 patient; 2.32%), streptococcal infection (1 patient; 2.32%), leukemia (1 patient; 2.32%), renal disease (1 patient; 2.32%), and severe tooth decay (1 patient; 2.32%). In 2 (4.65%) patients, there were no systemic diseases except immunoglobulin deficiency (1 selective immunoglobulin A deficiency, 1 Bruton's agammaglobulinemia). These patients belong to the group of uveitis that are related to systemic diseases (Table 1).

Anterior uveitis was the most common clinical form that involved 43 (67.19 %) eyes. Eight eyes (12.50%) had intermediate uveitis, 3 (4.69%) had posterior uveitis, and 10 (15.62%) had panuveitis (Table 2). Localization of uveitis in association with etiology is shown in Table 3. The mean number of recurrent uveitis attacks in our patients was 2.60±2.50 (1-12). VA was <20/40 in 12 (30%) of the 40 eyes which had more than one uveitis attacks. The increased number of attacks may result in worse visual outcome, but there was no statistically

significant relation ($p=0.277$, $r=0.14$; Spearman's correlation analysis) (Figure 1).

VA was inexpressive in a 3-year-old boy with bilateral anterior uveitis. At the last visit, VA was worse than 20/200 in 4 (6.25%) eyes and worse than 20/40 in 18 (28.12%) eyes. VA improved or remained stable in 45 (72.58%) eyes and decreased in 17 (27.42%) eyes. Mean VA was converted to logMAR equivalent for statistical analysis. Mean VA improved from 0.28 ± 0.34 (0-1.3) (LogMAR) to 0.15 ± 0.24 (0-1.0) (LogMAR), and the difference was statistically significant ($p<0.001$, $r=0.5$, Spearman's correlation analysis) (Figure 2). Of the 17 eyes which experienced VA decrease, 9 (52.94%) were with anterior, 3 (17.65%) with intermediate, 1 (5.88%) with posterior uveitis, and 4 (23.53%) were with panuveitis according to anatomical location (Figure 3). Although it seems that anterior uveitis was the most vision-threatening location, there was no statistically significant relation between anatomical location of uveitis and final visual outcome ($p=0.22$, Mann-Whitney U-test).

Etiology	Patients n (%)
JIA	5 (11.63)
Behcet's disease	4 (9.3)
HSV infection	2 (4.65)
Toxoplasma infestation	1 (2.32)
Streptococcal infection	1 (2.32)
Leukemia	1 (2.32)
Renal disease	1 (2.32)
Tooth decay	1 (2.32)
Ig deficiency	2 (4.65)
Idiopathic	25 (58.14)
Total	43

JIA: Juvenil Idiopathic Arthritis
 HSV: Herpes Simplex Virus
 Ig: Immunoglobuline

Localization	Eyes (n)	Eyes (%)
Anterior	43	67.19
Intermediate	8	12.5
Posterior	3	4.69
Panuveitis	10	15.62
Total	64	100

We evaluated some factors that could be related to final VA. Although it seemed that uveitis in patients with accompanying systemic disorder resulted in worse final VA, there was no statistically significant association between etiology of uveitis and final visual outcome ($p=0.688$, Mann-Whitney U-test) (Figure 4). Also, age at diagnosis did not have any significant correlation with final VA ($p=0.267$; $r=0.021$, Spearman's correlation analysis). Additionally, there was no statistically significant correlation between duration of uveitis and final VA ($p=0.517$; $r=0.082$, Spearman's correlation analysis).

Complications were noted in 16 (25%) of the 64 eyes. These complications included glaucoma in 8 (12.50%) eyes, cataract in 4 (6.25%), epiretinal membrane in 2 (3.12%) eyes, and band keratopathy, vitreous opacification and tractional retinal detachment in 1 (1.56%) eye each. Cataract developed in the left eye of a patient with bilateral glaucoma. All the 4 patients who developed glaucoma had been treated with topical steroids, while 3 of them had been treated with systemic steroids additional to topical treatment. Cataract developed in 4 patients who had been treated with topical steroids and 3 of these patients had used systemic steroids additional to topical treatment also. Table 4 presents the complication rates during the follow-up of these eyes.

Complications occurred in 10 (23.25%) of the 43 eyes with anterior uveitis, in 4 (50%) of the 8 eyes with intermediate

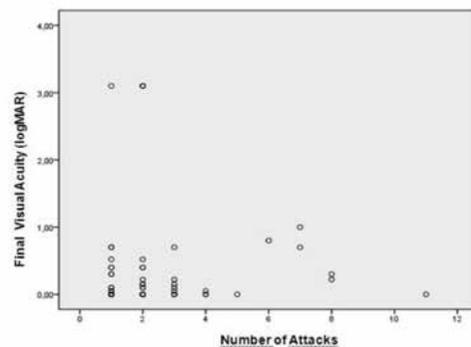


Figure 1. Correlation between recurrence and visual acuity (Spearman's correlation analysis, $p=0.277$, $r=0.14$)

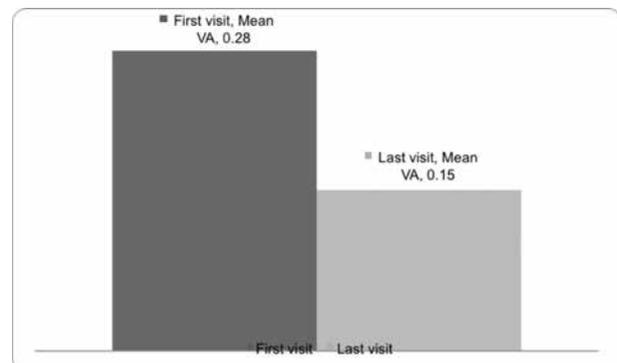


Figure 2. Visual acuity changes in pediatric uveitis

* Spearman's correlation analysis ($p<0.001$)

Etiology	Anterior patients n (%)	Intermediate patients n (%)	Posterior patients n (%)	Panuveitis patients n (%)
JIA	4 (9.3%)	-	1 (2.32%)	-
Behcet's disease	1 (2.32%)	-	-	3 (6.97%)
HSV infection	2 (4.65%)	-	-	-
Toxoplasma infestation	-	-	1 (2.32%)	-
Streptococcal infection	1 (2.32%)	-	-	-
Leukemia	1 (2.32%)	-	-	-
Renal disease	1 (2.32%)	-	-	-
Tooth decay	1 (2.32%)	-	-	-
Ig deficiency	2 (4.65%)	-	-	-
Idiopathic	18 (41.86%)	5 (11.63%)	-	2 (4.65%)
Total	31 (72.09%)	5 (11.63%)	2 (4.65%)	5 (11.63%)

JIA: Juvenil Idiopathic Arthritis
 HSV: Herpes Simplex Virus
 Ig: Immunoglobuline

Complication	Number of Eyes n= 64 (%)
Glaucoma	8 (12.5)
Cataract	4 (6.25)
Epiretinal membrane	2 (3.12)
Band keratopathy	1 (1.56)
Vitreous opacification	1 (1.56)
Tractional retinal detachment	1 (1.56)

uveitis, and in 2 (20%) of the 10 eyes with panuveitis. Complication frequencies significantly increased with increasing number of recurrent attacks ($p=0.046$; independent t-test). Four (16.66%) of the 24 eyes which had just one uveitis attack developed complications; whilst 12 (30%) of the 40 eyes that had more than one uveitis attack developed complications.

Of the 64 eyes, 33 (51.56%) underwent local and 31 (48.44%) underwent combined local and systemic treatment. We saw that 12 (75%) of the 16 eyes who developed any complication had both topical and systemic treatment (Table 5).

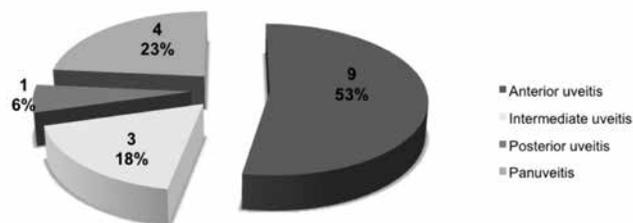


Figure 3. Anatomical distribution of the 17 eyes that experienced visual acuity decrease

There was a trend to cases under topical and systemic treatment having a higher risk than the cases under only topical treatment in respect to complication. But the difference was not statistically significant ($p=0.152$, Fisher's exact test)

Discussion

Pediatric uveitis is an entity that accounts for 5-10% of overall uveitis patients in referral centers.^{2,3} Pediatric uveitis cases accounts for 2.14% of all uveitis patients from all age

Type of treatment	Complication (+) Eyes n (%)	Complication (-) Eyes n (%)	Total
Topical	4 (6.25%)	29 (45.31%)	33 (51.56%)
Topical+systemic	12 (18.75%)	19 (29.69%)	31 (48.44%)
Total	16 (25%)	48 (75%)	64 (100%)

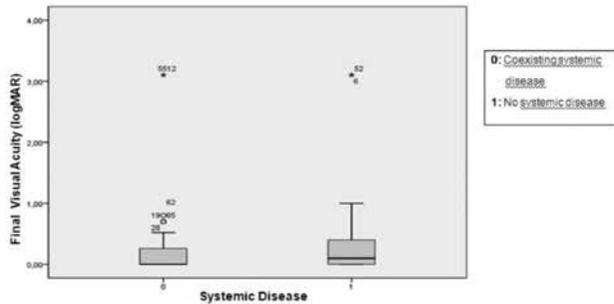


Figure 4. The effect of coexisting systemic diseases on final visual acuity in pediatric uveitis. (Mann-Whitney U-test, p=0.168)

groups in our Uveitis Unit. This rate is similar to other referral centers. The diagnosis and treatment of uveitis in pediatric age group is challenging.¹⁰ Diagnosis often is delayed because of relatively few symptoms and failure to verbalize the complaints of inflammation such as changes in vision by small children. The relatively high rate of complications, compliance with treatment and side effects of the local and systemic treatment poses unique challenges in the pediatric age group.⁸

Unilateral involvement was seen mostly in our series. However, previous studies report bilateral involvement mostly in pediatric uveitis.^{2,8,11-13} This may be due to the small sample size of our study group.

In the present study, we reported that the most common type of uveitis in pediatric patients was anterior uveitis (67.19%), followed by panuveitis (15.62%). This was similar to some recent reports.^{7,8,12,14} But in a report from Southern Turkey, Soyly¹⁵ noticed that anterior and panuveitis had almost the same frequency (33.3%, 34.4%) and in another report by Kadayifcilar,¹⁶ anterior uveitis was the most common form but was followed by posterior uveitis. Also, there are reports notifying that intermediate uveitis was the most common form in their series.¹¹ They reported high rates of intermediate uveitis such as 41.7% and 43.47% respectively; these rates are much higher than that in our series. Differences in geographic and ethnic origin of the patients may play a role in variable expression of the disease and may account for the conflicting results in the literature.

Intraocular inflammation was idiopathic in 58.14% of our patients; this finding was comparable with the report by Kazokoglu.¹⁸ It was a comprehensive study participated by eight university clinics. The authors reported that 58.3% of uveitis was idiopathic in pediatric patients. In that report, the

most common etiological entities in pediatric uveitis were JIA(12.50%), ocular toxoplasmosis (12.50%) and Behcet’s disease (0.40%). In our study, JIA (11.63%) followed by Behcet’s disease (9.50%) was the most commonly identified entity related to uveitis in children. In another report by Tugal-Tutkun,⁶ uveitis associated with JIA was the largest group (41.5%) in pediatric population. Sızmaç¹⁹ reported that Behcet’s disease (33.3%) and the JIA (25%) were the most common etiologies in their series of 11 patients, similar to our series. Khairallah²⁰ contrary to our study, reported that JIA was seen in only 6.25% of pediatric uveitis patients. In 2 cases in which we could not find any systemic etiologic reason, we detected immunoglobulin deficiency (1 selective immunoglobulin A deficiency, 1 Bruton’s agammaglobulinemia). Kubicka-Trzaska²¹ reported that they have detected immunological abnormalities in 38 of 50 cases (76%) with idiopathic posterior uveitis. Also, there are reports pointing out that common variable immunodeficiency (CVID) can be associated with chronic anterior uveitis.²² Because of good response to intravenous immunoglobulin therapy in patients unresponsive to conventional immunomodulatory agents, it is thought that non-specific abnormalities of immune system parameters can play a role in pathogenesis of uveitis.^{23,24} Besides this, there is a study from Turkey which reported no idiopathic case in their series of 23 patients.¹⁷

Tugal-Tutkun²⁵ reported that panuveitis in childhood-onset uveitis related to Behcet’s disease was the most common form (86.2%). In our study, 75% of patients related to Behcet’s disease had panuveitis.

Infectious uveitis accounts for 3-50% of inflammatory involvement for all age groups. In developed countries, toxoplasmosis and HSV were the most common agents, whilst in developing countries toxoplasmosis, onchocerciasis, HSV, tuberculosis, and leptospirosis were predominating.¹ In our study, intraocular inflammation was infectious in only 11.63% of cases. In a study from South Turkey, the authors reported that 42.3% of childhood uveitis that could be associated to any condition was infectious.¹⁵ It has been reported that uveitis in pediatric and adolescents associated with an infectious agent was 33.3% in a previous study.¹¹ Authors appointed that uveitis in children was mostly infectious (54.9%) in a report from India.¹ Toxoplasmosis was seen in 4.7% (29 patients) of patients in that study. In our study, toxoplasma uveitis was diagnosed only in 1 (2.32%) case. The difference between that study and ours is not limited only about infectious cases, they did not meet any Behcet’s uveitis in children oppositely to our series. In many of previous studies,

the incidence of toxoplasmic uveitis was common than our report. In a report from our country, toxoplasmosis presented in 39% of the 59 patients in whom an associated condition could be found.¹⁵ Environmental, geographical, cultural and socioeconomical factors such as cooking regimens and hygiene practice could clarify the variation of infectious uveitis in almost different regions of the same country.

Mean VA improved from presentation to the last visit from 0.28 ± 0.34 (0-1.3) (LogMAR) to 0.15 ± 0.24 (0-1.0) (LogMAR), and the difference was statistically significant in our study. VA improved or remained stable in 45 (72.58%) eyes and decreased in 17 (27.42%) eyes. There was no statistically significant association between anatomical location of uveitis and final visual outcome.

In this study, glaucoma and cataract formation were seen in 12.50% and 6.25% of eyes, respectively. Tugal-Tutkun²⁵ reported that they met glaucoma in 12.12% of 36 eyes in children with Behcet's disease, a similar ratio with our patients. In contrast to our study, they reported cataract formation in 46.9% of eyes. This high appearance of cataract formation might be resulted from high ratio of panuveitis (86.2%) and the use of systemic steroids in this patients.

Rosenberg¹² reported that panuveitis followed by intermediate uveitis have the highest risk for complications. Although there was no statistically significant association, it seems that patients with intermediate uveitis followed by anterior uveitis tended to have complications more than other locations in our study group. We attribute that high complication rates in anterior and intermediate uveitis groups to relatively few symptoms, late referral to a specialist, and delay of diagnosis. We thought that rigorous course of posterior uveitis may cause early referral and aggressive treatment, especially well-known situations such as Behcet's disease in our country, so complications occur rarely in these groups.

Although the difference was not statistically significant, there was a trend for cases under systemic treatment to have a higher risk to develop complications than the cases under only topical treatment. This was thought to be due to the fact that patients who underwent systemic treatment had already serious ocular involvement. Severe visual complications oriented us towards aggressive therapy in childhood uveitis. When prescribing topical or systemic steroids, side effects must be kept in mind. Besides the effects on intraocular pressure and cataract formation especially, systemic steroids have side effects such as osteoporosis, Cushing syndrome, and growth retardation in pediatric population, as distinct from adults. We could not determine any statistically significant association between anatomical location of uveitis and final visual outcome. Discordant to our report, Edelsten²⁶ reported that patients with posterior uveitis had worse visual outcomes. Also, Rosenberg¹² reported that anterior uveitis tended to have better visual prognosis than other locations. This distinction might be caused by our small sample size or non-homogenous sample groups.

Although it seemed that uveitis patients with accompanying systemic disorder have poor visual prognosis, there was no statistically significant association between etiology of uveitis and final visual outcome. Also, age at referral and duration of uveitis did not have any significant correlation with final VA.

Shortening the time of referral to an uveitis service provides early diagnosis and prevents children from complications of both uveitis and treatment. Families may refer to pediatricians or general practitioner before an ophthalmologist when their children have complaints related to eyes. Therefore, other physicians must be alert about symptoms of uveitis in children and send them to an ophthalmologist earlier.

Our data is based on a university-based subspecialty clinic, so that it may reflect higher rates than expected. Especially the high rates of serious complications may be caused by referral of complicated pediatric patients to the university clinic. Despite new diagnostic techniques, idiopathic uveitis is still the most common diagnosis. We need collaborative management with pediatricians, rheumatologists, and ophthalmologists in childhood uveitis to prevent or minimize the complications and to get a favorable final visual outcome. Timely referral to uveitis specialists may lead to improve visual outcome in children. Proper management of pediatric uveitis is very important in achieving good VA. Through effective treatment, the visual prognosis appears to be good even in patients with severe involvement.

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