·Clinical Research·

Clinical characteristics of intermediate uveitis in adult Turkish patients

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Abstract

• AIM: To describe the clinical characteristics of Turkish patients with intermediate uveitis (IU) and to investigate the effect of clinical findings and complications on final visual acuity (VA).

• METHODS: We retrospectively analyzed the medical records of patients with IU who had at least 6mo of follow-up and were older than 16y.

• RESULTS: A total of 78 eyes of 45 patients were included in the study and the mean follow-up period was 19.4mo. The mean age at the time of presentation was 42.9s. Systemic disease associations were found in 17.7% of cases; sarcoidosis (8.8%) and multiple sclerosis (6.6%) were the most common diseases. Recurrence rate (odds ratio=45.53; 95%CI: 2.181-950.58), vitritis equals to or more than 3+ cells (odds ratio =57.456; 95%CI: 4.154-794.79) and presenting with VA less than 20/40 (odds ratio =43.81; 95% CI: 2.184 -878.71) were also found as high risk factors for poor final VA. At the last follow-up examination, 67.9% of eyes had VA of 20/40 or better.

• CONCLUSION: IU is frequently seen at the beginning of the fourth decade of life. The disease is most commonly idiopathic in adult Turkish patients. Patients with severe vitritis at presentation and patients with frequent recurrences are at high risk for poor visual outcome.

• **KEYWORDS:** intermediate uveitis; Turkish; adult

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INTRODUCTION

Intermediate uveitis (IU) is a type of uveitis that the primary site of the inflammation is the vitreous. The prevalence of IU varies in different populations and accounts for 6%-15% of all uveitis cases[1-4]. It is predominantly seen in the third and fourth decade of life. The etiology of IU is not completely understood and it has been reported to be idiopathic in most studies [1,4,5]. However, in some cases, systemic infections (*e.g* lyme, syphilis, tuberculosis) or non-infectious diseases (*e.g* multiple sclerosis and sarcoidosis) may be the underlying cause. Differences are seen between children and adults in respect to the etiology of IU. The systemic associations of IU are very rare in childhood.

Although IU is considered to be a benign form of uveitis, the chronic course and the complications of the disease may lead to poor visual outcome if not treated properly on time. The aim of the present study is to describe the etiological spectrum, clinical characteristics, course, and complications of adult Turkish patients with IU and to assess the effect of clinical findings and complications on final visual acuity (VA).

SUBJECTS AND METHODS

According to the diagnostic criteria of standardization of uveitis nomenclature (SUN) Working Group, IU should be used for subgroup of uveitis where vitreous is the major site of inflammation and the presence of peripheral vascular sheathing and macular edema should not change the classification [6]. We analyzed the medical records of patients with a diagnosis of IU, based on the diagnostic criteria of the SUN Working Group. Inclusion criteria were age older than 16y and a follow-up period of at least 6mo. Five hundred and ninety eight consecutive patients with uveitis were seen at the Uveitis Service of the Ophthalmology Clinic, Umraniye Training and Research Hospital from January 2009 to June 2013. Of total 598 patients, 56 (9.4%) were diagnosed with IU. Of these 56 patients, 45 fulfilled the inclusion criteria. An informed consent was obtained from all patients. The ethics committee approval was obtained for the purpose of this study.

Patient's demographics, ocular findings at presentation, complications which were seen during the follow-up and the associated systemic diseases were reviewed from the records.

All patients underwent a complete ophthalmic examination including best corrected VA, slit-lamp biomicroscopy, tonometry and posterior segment examination. At presentation, VISUCAM ® NM/FA (Carl Zeiss Meditec, Germany) fluorescein angiography (FA) was performed on all patients without dense media opacities. Optical cohorence tomography (OCT) device (RTVue-100 Optuvue Inc., Fremont, CA, USA) and ocular ultrasonography tests were performed when indicated.

Cystoid macular edema (CME), cataract, optic disc edema, glaucoma or ocular hypertension, posterior synechiae, epiretinal membrane, peripheral neovascularization, retinal breaks and retinal detachment were the ocular complications recorded in the study. Patients with CME which was seen ophthalmoscopically, underwent spectral domain OCT (SD-OCT) or FA. During follow-up, every patient with visual loss underwent SD-OCT to document the possible CME or macular thickening even though CME or macular thickening were not observed clinically. Intraocular pressure (IOP) greater than 21 mm Hg was defined as ocular hypertension. If associated optic disc or visual field damage were present, it was defined as glaucoma secondary to uveitis.

Laboratory investigations including complete blood count, sedimentation rate, angiotensin converting enzyme, serum lysozyme, purified protein derivative skin test, and venereal disease research laboratory test and imaging studies including thorax computerized tomography (CT) and magnetic resonance imaging (MRI), were conducted on all patients. Additional laboratory tests such as Borrelia serology, Bartonellae henselae serology or human leukocyte antigen (HLA) typing were performed when necessitated in cases of clinical suspicion. Systemic disease associations were consulted with an internist, rheumatologist or pulmonologist in order to document the etiological diagnosis. We evaluated ocular inflammation as idiopathic IU when an etiologic diagnosis could not be established.

In unilateral cases or in cases with CME, periocular or intravitreal steroid injections were administered as the first line therapy. The response of periocular or intravitreal steroid injections was evaluated with SD-OCT in patients with CME. Systemic corticosteroids (0.5-1 mg/kg/d) were required when periocular or intravitreal steroid injections remained insufficient or in cases with bilateral involvement. Immunosuppressive agents including azathioprine, cyclosporine and methotraxate were initiated as a steroid sparing drug or when steroids failed to suppress inflammation. In cases with associated anterior uveitis topical steroids (topical prednisolone acetate) were initiated. Pars plana vitrectomy was applied to manage complications such as retinal detachment. Visual improvement was defined as the gain of at least two lines of Snellen acuity. The effects of ocular findings and complications on final VA were analyzed statistically.

Statistical analysis was made using NCSS (Number Cruncher Statistical System) 2007&PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) programmes. Student's t-test was used in the comparison between two groups of parameters showing normal distribution and the Mann-Whitney U test was used for those parameters not showing normal distribution. In the comparison of qualitative data, Fisher's exact test and Yates' continuity correction test (Yates corrected Chi-square) were used. Backward Stepwise (conditional) Logistic Regression Analysis was used in the evaluation of risk factors affecting VA. Levels of significance were accepted as $P<0.05$.

RESULTS

All patient charts were reviewed. A total of 78 eyes of 45 patients, 32 females (71.1%) and 13 males (28.9%) were included in the study. The mean follow-up period was 19.4 mo (range 6-49mo; ±15.2). The mean age at the time of presentation was 42.9y (range 18-75y; ±15.0). Of these patients 33 (73.3%) had bilateral and 12 (26.7%) had unilateral involvement. Demographic characteristics of the patients are summarized in Table 1. Complaints at presentation were blurred vision in 31 patients (68.9%), floaters in 10 patients (22.2%), pain in 10 patients (22.2%), redness in 11 patients (24.4%) and photophobia in 1 patient (2.2%). The most common ocular findings at presentation were vitritis (100%), snowballs in 50 (64.1%) eyes, and snowbanking in 15 (19.2%) eyes and vasculitis in 16 (21.1%) eyes. Associated anterior segment inflammation was noted in 43 (55.1%) eyes.

Systemic disease association was found in 8 (17.8%) patients. Four (8.8%) patients had biopsy-proven sarcoidosis, 3 (6.7%) patients had multiple sclerosis (MS) and 1 (2.2%) patient had tuberculosis. Patient diagnosed with TB, received anti-tuberculosis therapy (ATT) in addition to systemic corticosteroids. In all these patients, the systemic diagnosis was made after ocular involvement. The most common complications during the follow-up period were CME in 46 (59.0%) eyes, cataract in 26 (33.3%) eyes, glaucoma or ocular hypertension in 17 (21.8%) eyes, and optic disc involvement in 17 (21.8%) eyes. The ocular complications are summarized in Table 2.

Systemic corticosteroids were administered to 28 (62.2%) patients and 9 (20%) patients received immunosuppressive agents. The vast majority of the patients treated with systemic corticosteroids and immunosuppressive agents had bilateral involvement. No significant difference in the recurrence rate was found between unilateral and bilateral involvement (Mann-Whitney U test, P=0.6) Anti-tuberculosis treatment was initiated in one patient diagnosed with tuberculosis. Of the 78 eyes, 49 (62.8%) received periocular or intravitreal steroid injections. The treatments which were given during

Table 1 Demographic characteristics of patients with intermediate uveitis

Parameters	Value
Mean age (a)	42.9 (range 18-75)
Gender, *n* (%)	
M	13 (28.9)
F	32 (71.1)
Mean follow-up (mo)	19.4 (range 6-49)
Ocular involvement, *n* (%)	
Unilateral	12 (26.7)
Bilateral	33 (73.3)

Table 2 Ocular complications of intermediate uveitis

Ocular complications	*n* (%)
Cystoid macular edema	46 (59.0)
Cataract	26 (33.3)
Optic disc involvement	17 (21.8)
Glaucoma or ocular hypertension	17 (21.8)
Posterior synechiae	10 (12.8)
Epiretinal membrane	8 (17.3)
Peripheral neovascularization	7 (9.0)
Retinal breaks	3 (3.8)
Retinal detachment	2 (2.6)

Table 3 Treatment of intermediate uveitis $\bar{x} \pm s$, *n* (%)

Treatment	Bilateral involvement (33 patients, 66 eyes)	Unilateral involvement (12 patients, 12 eyes)
Systemic corticosteroids (oral prednisolone)	24 (72)	4 (33.3)
Mean duration of oral prednisolone treatment (mo, range)	16.5 (1-47)	15 (6-36)
Immunsuppressant treatment	8 (24.2) [a]	1 (8.3) [b]
Mean duration of immunsuppressent treatment (mo, range)	23.2 (10-47)	33 (18-42)
Subtenon/intravitreal/steroid injections	38 (57.5)	11 (91.6)
Mean no and range of periocular/intravitreal steroid injection per eye	1 (0-4)	1 (0-4)
Recurrence rate during follow-up, (median)	1.38±1.71 (1)	1.39±1.26 (1)
Mean follow-up duration (mo)	20.6±14.9 (6-47)	19.6±15.2 (6-48)

[a]There are 2 patients on azathioprine, 3 on cyclosporine, 2 on both azathioprine and cyclosporine and 1 on methotrexate; [b]Azathioprine.

the follow-up were shown in Table 3. Sixteen eyes underwent cataract surgery with intraocular lens implantation and one eye underwent pars plana vitrectomy for retinal detachment. Three eyes underwent laser photocoagulation for peripheral neovascularization in 2 eyes and retinal break in one eye.

The mean VA at presentation was 20/50 (range 20/20-counting fingers). At the final follow-up, VA had improved in 46 (59.0%) eyes, deteriorated in 10 eyes (12.8%) and remained the same in 22 (28.2%) eyes. Of these 78 eyes, 53 (67.9%) had final VA of 20/40 or better. The mean final VA was 20/32 (range 20/20-20/400).

The effect of ocular findings and ocular complications on final VA were also assessed. Final VA less than 20/40 was found to be significantly associated with presenting with VA of less than 20/40 (P=0.001), vitritis equals to or more than 3+ cells (P=0.001), snowbanking (P=0.001), CME (P=0.001), cataract (P=0.001) and ERM (P=0.001). Recurrence rate (odds ratio=45.53, 95%CI: 2.181-950.58), vitritis equals to or more than 3+ cells (odds ratio =57.456; 95% CI: 4.154-794.79), and presenting with VA worse than 20/40 (odds ratio=43.81; 95% CI: 2.184-878.71) were found as increased risk factors for poor visual outcome. Details were given in Tables 4, 5.

Table 4 Final visual acuity based on recurrence rate, initial visual acuity, ocular findings $\bar{x} \pm s$, *n* (%)

Variables	Final VA		*P*
	≥20/40 (*n*=53)	<20/40 (*n*=25)	
Recurrence rate (median)	1.00±1.14 (1.0)	2.20±1.41 (2.0)	[1]0.001[a]
Snowball	29 (58)	21 (42)	[2]0.030[a]
Vasculitis	14 (87.5)	2 (12.5)	[3]0.125
Anterior uveitis	38 (63.3)	22 (36.6)	[2]0.191
Snowbanking	4 (26.6)	11 (73.3)	[3]0.001[a]
Vitritis≥3	4 (20)	16 (80)	[2]0.001[a]
Initial VA			
VA≥20/40	36 (94.7)	2 (5.2)	0.001[a]
VA<20/40	17 (42.5)	23(57.5)	

VA: Visual acuity; [a]Statisitically significant; [1]Mann-Whitney *U* Test; [2]Yates' continuity correction Test; [3]Fisher's exact test.

Table 5 Final visual acuity based on complications *n* (%)

Complications	Final visual acuity		*P*
	VA≥20/40 (n^1=53)	VA<20/40 (n^1=25)	
Cystoid macular edema	24 (52.1)	22 (47.8)	[2]0.001[a]
Cataract	7 (26.9)	19 (73)	[2]0.001[a]
Opticdisc involvement	10 (58.8)	7 (41.1)	[2]0.537
Epiretinal membrane	4 (22.2)	14 (77.7)	[2]0.001[a]
Retinal break	1 (33.3)	2 (66.6)	[3]0.239
Retinal neovascularization	3 (42.8)	4 (57.1)	[3]0.202
Retinal detachment	0 (0.0)	2 (100)	[3]0.100

[1]No. of eyes; [2]Yates' continuity correction test; [3]Fisher's exact test; [a]Statisitical significant.

DISCUSSION

In this study, we intended to show the demographic and the clinical characteristics of IU in adult Turkish patients. IU is mostly seen as a bilateral disease and the bilateral involvement has been reported at rates ranging from 67% to 80% in several studies [1,3,7,8]. The percentage of bilateral cases in the current study was 73%, which is in line with the

previous data. The percentage of females in our study was 71.1%. It was reported as 55%-61% in different studies[7], but those reports evaluated children and adults together. In pediatric cases, IU is seen more frequently in males, which may explain the higher rate of female patients in our study. The mean age at presentation was found as 42.9y (range 18-75y); as expected this result is higher than the mean age in other studies where children and adults were evaluated together[1,4].

In several studies, IU cases have been reported as idiopathic at high rates [9-15]. Similarly, in our study 83.7% of cases were idiopathic. The most specific diagnosis in the current cases was sarcoidosis at a rate of 8.8%. Similary to our result in several studies, sarcoidosis has been observed at rates of 4%-8% [1,4,5]. In the present study, none of the cases with sarcoidosis had an established diagnosis of systemic sarcoidosis at presentation. This finding shows the importance of investigating the etiology of sarcoidosis in IU patients.

The other specific diagnosis seen in IU etiology is MS. MS has been reported in IU patients at 3%-17% [3,4,13]. Previous studies suggested that MS could be diagnosed in IU patients during follow-up period [12,16]. In our study, MS was observed at a percentage of 6.6% whereas in a recent study with a longer follow-up period, MS was reported as the most frequently associated systemic disease in adults at rates of 18.6% [15]. Besides differing referrals, our shorter follow-up period might explain the differences in MS rates between two studies. Probability of MS development in IU patients highlights the importance of neurological monitoring during the follow-up. Supporting this finding, one of our patients was diagnosed with MS by repeated neurological imaging at the second year after presentation.

Systemic corticosteroid therapy was applied to 62.2% of the cases in the present study. For the 20% of the cases who required long-term corticosteroid therapy and those who showed frequent recurrence were treated with immunosuppressive therapy. Previous studies have reported the application of systemic corticosteroid therapy in 40%-60% of IU patients and immunosuppressive therapy in 15%-20%[1,3]. Periocular or intravitreal steroid injections were preferentially used in unilateral cases whereas systemic corticosteroids and immunosuppressive agents in bilateral cases. However, intravitreal and periocular steroid usage rates were not different between unilateral and bilateral cases. Although immunsuppresive treatment was used more frequently in patients with bilateral involvement, no significant difference was found between recurrence rates of patients with unilateral and those with bilateral involvement during follow-up. This may be explained by the severe nature of the uveitis in patients who received immunosuppression treatments.

The most common complications were CME (59.0%), cataract (33.3%) and optic disc involvement (21.8%). In previous studies, CME has been reported at rates of 28%-64% and cataract 30%-35% [4,7,17] and these rates conform with the current findings. Several ocular findings and complications were reported as poor prognostic factors for final VA in different studies. In a recent study, poor VA at presentation and snowbanking were found to be increased risk factors for poor final VA. Khairallah *et al* [4] reported vitritis more than 3+ cells as a poor prognostic factor in their study. We found presenting VA less than <20/40, recurrence rate and vitritis equals to or more than 3+ cells as increased risk factors for poor visual outcome in our study. We consider that severe vitritis is associated with a recurrent and more severe disease and may show resistance to both systemic and local therapy.

Even though it is rare, retinal detachment or retinoschisis may develop in IU patients [7,18]. We observed 2 cases with retinal detachment. One of these cases was diagnosed with sarcoidosis and other cases had localized tractional retinal detachment. Similarly, non-progressive tractional retinal detachment has been reported in IU patients [19]. As there was no macular involvement in our case, the patient was only observed without intervention. In the other case diagnosed with idiopathic IU, rhegmatogenous retinal detachment developed following a severe vitritis attack and pars plana vitrectomy surgery was applied to this patient.

Despite these complications, the 68 % of the eyes had a good visual prognosis where the VA was 20/40 and above. Supporting our findings, it has been reported that with appropriate treatment, the vision in 70% of IU patients remain at 20/40 and above[10,12].

According to our knowledge, this is the first report from Turkey which investigates the patients with IU in adult age. In the present study, IU was seen at the beginning of the fourth decade of life and was often bilateral. Although the vast majority of our cases were idiopathic, sarcoidosis and MS should be kept in mind as etiological diagnoses. The most common complications were CME and cataract. Visual prognosis was good for most cases with the appropriate medical and surgical treatment. However, severe vitritis at presentation and high recurrence rates were found as increased risk factors for poor visual outcome. In these subgroup patients, early and aggressive treatment strategies may enable more effective control of the inflammation which can reduce recurrence rates and further complications.

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REFERENCES

1 Chan CK, Wu ZH, Luk FO, Liu DT, Fan AH, Lee VY, Lai TY. Clinical Characteristics of Intermediate Uveitis in Chinese Patients. *Ocul Immunol Inflamm* 2013;21(1):71-76

2 Kazokoglu H, Onal S, Tugal-Tutkun I, Mirza E, Akova Y, Ozyazgan Y, Soylu M, Batioglu F, Apaydin C. Demographic and clinical features of uveitis in tertiary centers in turkey. *Ophthalmic Epidemiol* 2008;15 (5): 285-293

3 Paroli MP, Abicca I, Sapia, Bruschi S, Pivetti Pezzi P. Intermediate uveitis: comparision between childhood-onset and adult-onset disease. *Eur J Ophthalmol* 2014;24(1):94-100

4 Khairallah M, Hmidi K, Attia S, Jelliti B, Hasnaoui W, Zaouali S, Jenzeri S, Yahia SB, Messaoud R. Clinical characteristics of intermediate uveitis in Tunisian patients. *Int Ophthalmol* 2010;30(5):531-537

5 Singh R, Gupta V, Gupta A. Pattern of uveitis in a referral eye clinic in north India. *Indian J Ophthalmol* 2004;52(2):121-125

6 Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol* 2005;140(3):509-516

7 Parchand S, Tandan M, Gupta V, Gupta A. Intermediate uveitis in Indian population. *J Ophthalmic Inflamm Infect* 2011;1(2):65-70

8 Kianersi F, Mohammadi Z, Ghanbari H, Ghoreyshi SM, Karimzadeh H, Soheilian M. Clinical Patterns of Uveitis in an Iranian Tertiary Eye-care Center. *Ocul Immunol Inflamm* 2014;16

9 Babu BM, Rathinam SR. Intermediate uveitis. *Indian J Ophtahlmol* 2010;58(1):21-27

10 Donaldson MJ, Pulido JS, Herman DC, Diehl N, Hodge D. Pars planitis: a 20-year study of incidence, clinical features, and outcomes. *Am J Ophthalmol* 2007;144(6):812-817

11 de Boer J, Berendschot TT, van der Does P, Rothova A. Long term follow-up of intermediate uveitis in children. *Am J Ophthalmol* 2006;141 (4):616-621

12 Vidovic-Valentincic N, Kraut A, Hawlina M, Stunf S, Rothova A. Intermediate uveitis: long-term course and visual outcome. *Br J Ophthalmol* 2009; 93 (4):477-80

13 Al-Mezaine HS, Kangave D, Abu El-Asrar AM. Patterns of uveitis in patients admitted to a University Hospital in Riyadh, Saudi Arabia. *Ocul Inflamm* 2010;18(6):424-431

14 Cimino L, Aldigeri R, Salvarani C, Zotti CA, Boiardi L, Parmeggiani M, Casali B, Cappuccini L. The causes of uveitis in a referral centre of Northern Italy. *Int Ophthalmol* 2010;30(5):521-9

15 Heinz C, Schoonbrood S, Heiligenhaus A. Intermediate uveitis in children and young adults: differences in clinical course, associations and visual outcome *Br J Ophthalmol* 2014;98(8):1107-1111

16 Karagiannis DA, Ladas ID. An unusual optic disc neovascularization in a case of intermediate uveitis associated with multiple sclerosis. *Eur J Ophthalmol* 2008;18(6):1020-1022

17 Taylor SR, Lightman SL, Sugar EA, Jaffe GJ, Freeman WR, Altaweel MM, Kozak I, Holbrook JT, Jabs DA, Kempen JH. The impact of macular edema on visual function in intermediate, posterior, and panuveitis. *Ocul Immunol Inflamm* 2012;20(3):171-181

18 Sizmaz S, Gungor SG, Bayar SA, Yilmaz G, Akkoyun I. Laser photocoagulation in intermediate uveitis associated with retinoschisis. *Ocul Immunol Inflamm* 2012;20(5):372-374

19 Jalil A, Dhawahir-Scala FE, Jones NP. Nonprogressive tractional inferior retinal elevation in intermediate uveitis. *Ocul Immun Inflamm* 2010;18(1):60-63