

Association between intermediate uveitis and toxocariasis in the Korean population

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Abstract

The aim of the study was to investigate the characteristics of ocular toxocariasis (OT) presenting with intermediate uveitis in the Korean population.

We studied intermediate uveitis patients using ocular and systemic evaluations and a *Toxocara* IgG serology test.

Of 50 intermediate uveitis patients, 19 were seropositive for *Toxocara* IgG. Of the 19 OT patients, 4 presented with recurrence within 6 months and were significantly younger than nonrecurrence patients ($P=0.009$). Thirteen patients had a history of eating raw cow liver.

There were 14 males and 5 females in the OT group, and 11 males and 20 females in the non-OT group ($P=0.009$). There was bilateral involvement in 7 out of 19 patients in the OT group, and 20 out of 31 patients in non-OT group ($P=0.033$).

Intermediate uveitis patients in OT were predominately male and had more unilateral presentation than non-OT patients.

Abbreviations: BCVA = best-corrected visual acuity, CME = cystoid macular edema, ELISA = enzyme-linked immunosorbent assay, Ig = immunoglobulin, IOP = intraocular pressure, log MAR = logarithm of the minimum angle of resolution, OCT = optical coherence tomography, OT = ocular toxocariasis, RM = epiretinal membrane.

Keywords: intermediate uveitis, ocular toxocariasis, raw cow liver

1. Introduction

Toxocariasis is a disease in humans caused by *Toxocara canis* or *Toxocara cati*.^[1–3] Based on the infected organs, it is clinically classified into visceral larva migrans, ocular larva migrans, and neurological larva migrans.^[4,5] Accidental ingestion of embryonated eggs or larvae through contact with puppies, or geophagia, has traditionally been considered the main infectious route.^[6–8] But recent studies from Asia have suggested that infection may be possible through the ingestion of raw cow liver or meat.^[9–13]

Ocular toxocariasis (OT) can induce inflammation of uveal and retinal tissues, and can result in diverse lesions, from a simple peripheral pigmentary retinal scar to macular damage that can cause severe visual loss after treatment.^[9,10,13,14] One previous study reported that 100% of OT patients presented with vitritis, and another study reported that 53% of OT patients complained of decreased visual acuity.^[15,16] We previously reported the clinical features of OT patients in 53 consecutive patients.^[13]

However, we only reported the diverse clinical presentations of OT and did not determine prevalence of OT in uveitis patients or the differentiating features from non-OT uveitis patients.

Hence, in this study, we determined the prevalence of OT in intermediate uveitis patients, monitored their progress after treatment, and identified the different clinical presentations between OT-related intermediate uveitis patients and non-OT-related intermediate uveitis patients.

2. Methods

The medical records of all patients diagnosed with intermediate uveitis at St. Vincent's Hospital, Suwon, Republic of Korea, between 2014 and 2016 were retrospectively reviewed. This study was performed according to the tenets of the Declaration of Helsinki, and the study protocol was approved by the institutional review/ethics boards of the Catholic University of Korea and our hospital. No informed consent was obtained because this study involved a chart review, and because patient records were anonymized prior to analysis.

All patients underwent a full ophthalmic examination, including measurements of best-corrected visual acuity (BCVA), refraction, and intraocular pressure (IOP); a dilated fundus examination after maximum pupil dilation; a complete blood count; blood chemistry analyses; tests for *Toxocara* IgG, *Toxoplasma* IgM, and IgG; assessment of total IgE levels; chest x-rays, measurements of HLA-B27, angiotensin converting enzyme, antinuclear antibody, hepatitis B surface antigen antibody, and anti-hepatitis C virus antibody levels; syphilis reagin tests; and a questionnaire about eating habits and whether patients had any pets. The *Toxocara* IgG test is a standard method for measuring antibody titers by an indirect enzyme-linked immunosorbent assay (ELISA) based on the *Toxocara* larvae crude antigen.^[17,18] Its sensitivity and specificity have been reported to be 92.2% and 86.6%, respectively.^[19] After all of these tests, all patients were

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examined by a rheumatology specialist to determine the cause of the intermediate uveitis.

Inclusion criteria included patients diagnosed with naive intermediate uveitis without retinal lesion and no known related disease until the first visit, with a follow-up of at least 6 months after the first diagnosis and treatment. All patients diagnosed with OT were treated with oral steroids with tapering in 2 months, and with 400 mg albendazole twice per day for 2 weeks to minimize recurrence.^[10]

We classified all intermediate uveitis patients who were seropositive for *Toxocara* IgG into the OT group, and those who were seronegative into the non-OT group. Sex distribution, age, bilaterality, IgE levels, eosinophil counts, and complications were compared between the 2 groups.

We analyzed the baseline clinical characteristics, IgE levels, eosinophil counts, suspected infection routes, optical coherence tomography (OCT) (Cirrus High Definition-OCT; Carl Zeiss Meditec, Dublin, CA) to check complications, changes in IOP and BCVA after treatment, and recurrence rates and complications like cystoid macular edema (CME) or epiretinal membrane (ERM) until 6 months in OT patients. After subgrouping OT patients based on the recurrence, we also compared the age, sex, IgE levels, and eosinophil counts between this subgroup.

The Wilcoxon signed-rank test was used to compare changes in IOP, and a paired *t*-test was used to compare changes in BCVA. The Mann-Whitney *U* test was used to compare age, IgE levels, eosinophil counts, BCVA, and IOP between the OT and non-OT groups. The Mann-Whitney *U* test was also used to compare age, IgE levels, and eosinophil counts in the OT subgroup.

The chi-square test was used to compare sex distribution and bilaterality between the groups. It was also used to compare the number of higher IgE levels (>100 IU/mL), and eosinophilia (eosinophil counts > 500/ μ L or > 5.0% of the total white blood cell count) in the recurrent and nonrecurrent OT groups.^[10,13,20] All statistical analyses were performed using SPSS statistical software for Windows, version 21.0 (SPSS, Chicago, IL). The statistical significance level was set at $P < 0.05$.

3. Results

Of 50 intermediate uveitis patients, 19 (38.00%) were seropositive for *Toxocara* IgG. In the non-OT group, 2 patients were diagnosed with Behcet's disease, 2 patient with sarcoidosis, 1 patient with rheumatoid arthritis, 1 patient with ankylosing spondylitis, 1 patient with inflammatory bowel disease, 1 patient with systemic sclerosis, and in 23 patients, we could not find any

disease related with intermediate uveitis, although they underwent a complete rheumatologic examination.

The initial IOP and BCVA (log MAR) of eyes with OT were 14.15 ± 4.58 mm Hg and 0.45 ± 0.43 , respectively, and the values at 6-month follow-up after treatment were 13.03 ± 2.95 mm Hg and 0.29 ± 0.28 , respectively ($P = 0.264$ and $P = 0.003$). The *P*-values in the box plots where median values were compared are not different from *P*-values in the text where mean values were compared (Fig. 1).

Regarding diet, 13 patients (68.42%) patients had a history of eating raw cow liver. Two patients had dogs and 1 had a cat. In the other 5 patients, an obvious infection route could not be identified. Of the 19 OT patients, 12 (63.16%) had higher IgE values than the normal range (>100 IU/mL) and only 4 (21.05%) had eosinophilia.

Four (21.05%) patients presented with recurrences at 6 months. The average age of recurrent patients was 43.75 ± 11.95 years and the average age of nonrecurrent patients was 60.33 ± 8.74 years; there was a significant difference between the 2 groups ($P = 0.009$). The level of IgE and count of eosinophil were not significantly different between the recurrent and nonrecurrent patients (348.00 ± 225.82 vs 426.40 ± 559.48 IU/mL, $P = 0.596$, 144.25 ± 109.34 vs 199.40 ± 142.07 , $P = 0.665$, respectively; Table 1).

Two (10.53%) OT patients showed cystoid macular edema and 2 (10.53%) OT patients had epiretinal membrane within 6 months.

There were 14 males (73.68%) and 5 (26.32%) females in the OT group, and 11 (35.48%) males and 20 females (64.52%) in the non-OT group ($P = 0.009$, odds ratio [OR] = 5.091). The average age was 56.84 ± 11.47 years in the OT group and 51.87 ± 16.72 years in the non-OT group ($P = 0.358$). The BCVA (log MAR) and IOP of involved eyes in the non-OT group were $0.26 \times 0.200A; \pm 0.40$ and 13.51 ± 3.52 mm Hg, respectively, with a significant difference compared with the OT group in BCVA, and no significant difference in IOP ($P = 0.003$ and $P = 0.701$, respectively).

Bilateral intermediate uveitis was diagnosed in 7 (36.84%) of 19 patients in the OT group, and 21 (67.74%) of 31 patients in the non-OT group, with a significant difference ($P = 0.033$). Of the 12 unilateral OT patients, 7 had uveitis in the right eye and 5 had it in the left eye.

The average IgE level in the OT group was 409.90 ± 503.02 IU/mL, and that of the non-OT intermediate uveitis group was 92.58 ± 149.80 IU/mL ($P = 0.002$). The average number of eosinophils ($/\mu$ L) in the OT group was 187.79 ± 135.00 and that in the non-

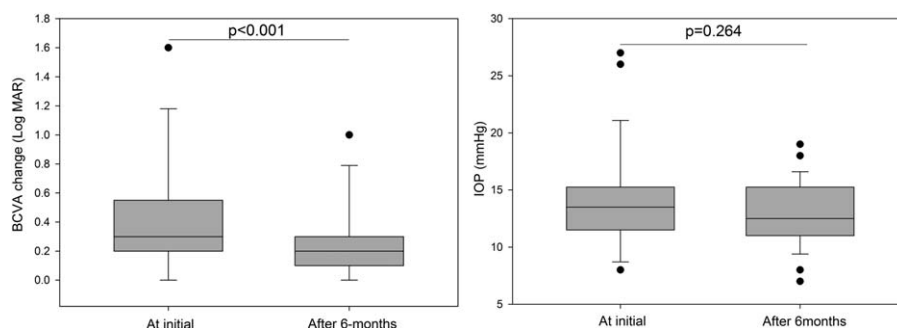


Figure 1. Changes in the best-corrected visual acuity (BCVA [log MAR], left) and intraocular pressure (IOP, right) in ocular toxocariasis patients. The dots represent outliers. The BCVA is increased after treatment with significant difference. And the IOP was decreased after treatment. But there is no significant difference. BCVA = best-corrected visual acuity, IOP = intraocular pressure, log MAR = logarithm of the minimum angle of resolution.

Table 1
Comparison of clinical characteristics according to recurrence at 6 months of OT.

	Recurrent cases	Nonrecurrent cases	P
Demographics			
Number	4 (21.05%)	15 (78.95%)	
Male:female	3:1	11:4	1.000
Age, y	43.75 ± 11.95	60.33 ± 8.74	0.009
Blood parameters			
Total IgE, IU/mL	426.40 ± 559.48	348.00 ± 225.82	0.596
Number with a high IgE, >100 IU/mL	3 (75.00%)	9 (60.00%)	
Eosinophil count, /μL	144.25 ± 109.34	199.40 ± 142.07	0.665
Eosinophilia, >500/μL or 5.0% >WBC	1 (25.00%)	3 (20.00%)	1.000

IU=intermediate uveitis, OT=ocular toxocariasis, WBC=white blood cells.

OT group was 106.71 ± 71.46 (P=0.010). The P-values in the box plots where median values were compared are slightly different from P-values in the text where mean values were compared. However, statistical significances were not different (Fig. 2). In the non-OT group, 2 patients had ERM and 2 had CME as complications at 6 months (Table 2).

4. Discussion

We report a possible association between toxocariasis and intermediate uveitis. Although some studies have reported intermediate uveitis in OT, our study is the first study to determine the prevalence of OT in intermediate uveitis.^[9,15,16] We first determined the differences in clinical presentation of OT-related uveitis and non-OT related uveitis.

Surprisingly, the most common cause of intermediate uveitis was OT in the Korean population. Only 8 patients were diagnosed with disorders associated with intermediate uveitis after rheumatological evaluations, and the cause could not be determined in 23 patients.

Moreover, there was a significant difference in sex distribution between the OT patients and the intermediate uveitis patients with other causes. The female predominance in adult-onset intermediate uveitis is consistent with a previous study.^[21] The OT group was predominately male. We suggest that this difference in sex distribution is caused by a history of eating

Table 2
Comparison of clinical characteristics according to the cause of intermediate uveitis.

	OT-related IU	Non-OT-related IU	P
Demographics			
Number	19	31	
Male:female	14:5	11:20	0.009
Age, y	56.84 ± 11.47	51.87 ± 16.72	0.358
Initial ocular examination			
BCVA, log MAR	0.45 ± 0.43	0.26 ± 0.40	0.003
IOP, mm Hg	14.15 ± 4.58	13.51 ± 3.52	0.701
Bilaterality, %	36.84	64.52	0.033
Blood parameters			
Total IgE, IU/mL	409.90 ± 503.02	92.58 ± 149.80	0.002
Number with a high IgE, >100 IU/mL	12 (63.16%)	5 (16.13%)	0.002
Eosinophil counts, /μL	187.79 ± 135.00	106.71 ± 71.47	0.010
Eosinophilia, >500/μL or 5.0% >WBC	4 (21.05%)	1 (3.23%)	0.062
Complications			
ERM	2 (10.53%)	2 (6.45%)	
CME	2 (10.53%)	2 (6.45%)	

BCVA=best-corrected visual acuity, CME=cystoid macular edema, ERM=epiretinal membrane, IOP=intraocular pressure, IU=intermediate uveitis, log MAR = logarithm of the minimum angle of resolution, OT=ocular toxocariasis, WBC=white blood cells.

raw cow liver. This possibility of relationships among OT, male sex, and raw cow liver has already been reported. Because some adult Korean men have been reported to eat raw cow liver, believing it to be healthy, which may have been the cause of OT in previous studies.^[10,12] Our study was consistent with these studies, showing a sex difference in the suspected route of infection. Of 5 female OT patients, only 2 had a history of eating raw cow liver. We could not find an obvious route of infection in the remaining 3 patients. However, of 14 male OT patients, 11 had a history of eating raw cow liver, and we could not find an obvious route of infection in only 2 patients.

This infection route also influences the age of onset of OT in the Korean population. In Western countries, OT is an important cause of pediatric uveitis, resulting from infection from a contaminated environment or from pets such as dogs and cats.^[4,22-25] In contrast, studies of the northeast Asian population have reported that young male adults have a higher prevalence of OT.^[10,26] We suggest that this resulted from the diets of young northeast Asian males, who tend to eat raw cow liver.^[10-12]

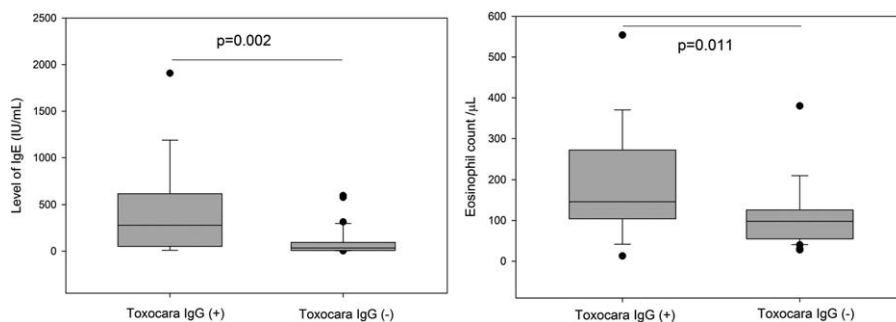


Figure 2. IgE levels (left) and eosinophil counts (right) in the ocular toxocariasis group and the intermediate uveitis group without toxocariasis. The dots represent outliers. There are significant differences between 2 groups in the level of IgE and eosinophil count.

In the analyses of intermediate uveitis patients with or without OT, the presence of bilateral ocular involvement was significantly different between the 2 groups. This phenomenon is consistent with previous studies that have reported that cases of intermediate uveitis without OT more frequently occur bilaterally in up to 81% of patients,^[21] whereas unilateral involvement is more common in OT patients.^[10,15] However, the cause of the more common unilateral involvement in OT patients versus intermediate uveitis patients is still unknown.

The IgE level of OT-related intermediate uveitis patients was significantly greater than that of non-OT-related intermediate uveitis patients ($P=0.002$). The eosinophil counts were also significantly different between the OT and non-OT groups ($P=0.010$). However, only 12 (63.16%) of 19 patients showed higher levels of IgE than the normal range, and eosinophilia was present in only 4 patients (21.05%). Therefore, we conclude that it is not possible to use IgE levels or eosinophilia as screening tests. Other studies have reported that total IgE levels were elevated in 69.6% and 77.3% of OT patients.^[10,13] Eosinophilia counts have also differed between studies; one study reported that abnormal eosinophilia counts were found in 66.7% of OT patients, whereas another study reported that 11.6% of OT patients showed abnormal counts.^[10,13] Regarding this large difference, we suggest that there was a difference in the definition of eosinophilia, and most patients in previous studies included many patients in the active uveitic phase with newly developed retinal granuloma lesions as an OT presentation, which might have involved more active immunological mechanisms. Therefore, we suggest that different inclusion criteria may result in differences in laboratory test results. Consistent with this possibility, although we did not analyze changes in IgE levels and eosinophil counts after treatment, many patients had dramatically lower levels.

The cases that showed recurrent OT at 6 months were significantly younger than patients without recurrence. We suggest that younger age may be associated with a strong immunological response that leads to recurrence within 6 months.

In terms of complications at 6 months, ERM occurred in 2 (10.53%) eyes and CME occurred in 2 (10.53%) eyes; these rates were lower in ERM and higher in CME than those reported in previous studies. The differences between studies may be due to differences in the follow-up durations and/or differences in the treatment regimens.^[10]

This study had some limitations. The sample size was small and the follow-up period was relatively short, so we plan to analyze additional cases over time and analyze them again several years later. In addition, there may have been selection bias involving the location of the study population, because our hospital was located in an urban area (Suwon, Republic of Korea). A previous study reported that there is a difference in prevalence by location of residence,^[10] but we did not survey this parameter. The ages of most patients (73.68%) were >50 years, and most patients experienced a change in location from rural to urban areas, but we did not take this change into account in our analyses. However, an accurate record of changes in living location may be helpful for tracing the infection route of OT. We also did not record data on ingestion of raw cow liver and meats, or ownership of pets in non-OT patients. In addition, although other studies used the aqueous humor or vitreous humor as samples for testing, or the Western blot technique for diagnoses,^[22,27,28] we detected IgG antibodies to *Toxocara* using only an indirect ELISA assay based on

the *Toxocara* larva antigen in blood samples.^[17,18] Analyses using additional samples or methods could have helped confirm our results.

In conclusion, the prevalence of OT was 38.00% in intermediate uveitis patients in the Korean population. In cases of intermediate uveitis, the possibility of OT should be considered, and knowledge of eating history and toxocariasis serological tests should be performed. Young patients have a higher recurrence rate, so they need careful observation and frequent follow-ups.

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