



Analysis of the clinical diagnosis and treatment of uveitis

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Background: Uveitis is a not uncommon potentially sight-threatening intraocular inflammatory disorder and a major cause of blindness worldwide. Early diagnosis and effective treatment are very important to reduce complications and protect vision.

Methods: In a retrospective series, we enrolled 263 (390 eyes) consecutive uveitis patients, comprising 126 males and 137 females. The clinical types of uveitis, treatment efficacy, complications and visual prognosis were evaluated by detailed clinical examination, laboratory tests and treatment observation.

Results: There were 101 cases of panuveitis (38.4%), 85 cases of anterior uveitis (32.3%), 75 cases of posterior uveitis (28.5%), and 2 cases of intermediate uveitis (8%). There was a statistically significant difference in (I) visual acuity between the acute and recovery periods ($F=13.12$, $P<0.05$); (II) visual acuity between first-time and recurrent patients ($F=9.26$, $P<0.05$); (III) visual acuity in the affected and healthy eyes in the total, anterior and posterior uveitis groups ($P<0.05$); and (IV) the presence of ocular complications. There was also a statistically significant difference in the presence or absence of ocular complications between patients with initial disease and those with a recurrence of disease ($F=59.51$, $P<0.05$).

Conclusions: In all its varying presentations, uveitis has a great impact on visual acuity. A careful clinical history should be taken and specific laboratory tests should be performed in order to improve the diagnosis and determine the etiology, and practitioners should provide appropriate treatment to avoid ocular complications, which can further damage visual acuity.

Keywords: Uveitis; diagnostics; treatments; outcomes; etiology

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Introduction

Uveitis is a not uncommon potentially sight-threatening intraocular inflammatory disorder that is a major cause of blindness worldwide (1,2). The incidence is 20–50/100,000/year and the prevalence is 100–150/100,000 (3). However, it varies in presentation and more contagious causes are found in less developed countries. Overall, uveitis causes 10–15% of global blindness, with 4–10% of patients

blinded by uveitis in China, and is the third leading cause of preventable blindness in the world (4,5). The etiology of uveitis is complex and varied, and the pathogenesis involves many aspects. Medical therapy is the cornerstone of the management of uveitis (6), because uncontrolled ocular inflammation can result in visually impactful ocular structural complications (7), and a significant risk of visual disability. Long-term treatment can have serious psychological, economic and quality-of-life consequences (8,9); if timely diagnosis and treatment

are not instituted, serious complications lead to irreversible damage of visual function. Clinicians should actively try to find the cause of uveitis to administer effective treatment, and for idiopathic uveitis, the best treatment plan to control the degree of inflammation and prevent complications and irreversible ocular structural damage and visual impairment should be selected according to the severity of the disease. We present the following article in accordance with the STROBE reporting checklist (available at <https://dx.doi.org/10.21037/apm-21-3549>).

Methods

Data collection

Between January 2018 to June 2021, 263 consecutive patients seen at the specialty uveitis clinic of the Tianjin Eye Hospital with various types of uveitis were enrolled. Detailed ocular and medical histories were obtained and the patients underwent routine slit lamp microscopy and fundus examinations, and tonometry to measure their intraocular pressure (IOP). Furthermore, 168 patients underwent fluorescein fundus angiography, ocular color fluorescein fundus angiography, ocular color Doppler examination and optical coherent tomography. Complete blood count, erythrocyte sedimentation rate, anti-chain "O", rheumatoid factor, antinuclear antibody, human leukocyte antigen (HLA)-27, chest or sacroiliac joint X-ray, skin mycotoxin tuberculosis testing, and syphilis and the blood HIV antibody testing were performed as needed. All patients were followed up for more than 6 months. Visual acuity examinations were recorded using the logMAR scale to determine the best corrected visual acuity of the patients. All participants gave their written informed consent. The study was approved by the Institutional Ethics Committee of Tianjin Eye Hospital (No. 2021023). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Clinical classification

The clinical classification and anatomically classified were based on the criteria of the International Uveitis Study Group, and the patients were classified as having anterior uveitis, intermediate uveitis, posterior uveitis or panuveitis according to the anatomic location. Based on the duration of the disease, acute uveitis was defined as duration of up to 3 months, chronic uveitis was defined as duration of more than 3 months, and recurrent uveitis was defined as the

disease being stable for more than 3 months (10).

Treatment

For mild anterior uveitis, topical glucocorticoids (0.5% tobramycin dexamethasone drops or 1% prednisolone acetate), compounded tropicamide to dilate the pupil and nonsteroidal anti-inflammatory (pralophine) drops were given, and a subconjunctival injection of dexamethasone sodium phosphate (3–4 mg) was given to patients with fibrin exudation in the anterior chamber. Patients with panuveitis and posterior uveitis were given oral prednisone tablets (0.8–1.0 mg/kg, decreasing every 7–14 days until discontinuation depending on the condition). For patients with contraindications to oral prednisone tablets or recurrent disease, treatment with an immunosuppressant, cyclosporine A or azathioprine, and systemic treatment with adalimumab or infliximab was given for severe ocular inflammation. Oral calcium tablets were given to patients taking oral prednisone tablets to prevent calcium loss, and the patients taking oral prednisone were also given gastric protection medication to reduce gastrointestinal reactions. Oral potassium chloride tablets were given to prevent hypokalemia in patients who had immunosuppressive therapy. During the treatment period, routine blood tests, including liver and kidney function, were regularly evaluated.

Statistical analysis

Statistical analysis was performed using SPSS 11.5. Univariate analysis was performed using the independent sample *t*-test for the visual acuity of the affected eyes in the acute recovery period, and ANOVA was performed to determine the differences between the groups of patients with initial and recurrent uveitis, anterior uveitis, posterior uveitis and total uveitis. Variables were analyzed by a 2×2 correlation using the Pearson correlation test. Statistical significance was defined as $P < 0.05$.

Results

Basic characteristics of the patients

The 263 patients with various types of uveitis included a total of 390 eyes. The mean age of onset was 44.62 ± 15.15 years (range, 4–75 years). There were 126 males, with a mean age of onset of 42.84 ± 15.82 years, and 137 females, with a mean age of onset of 46.25 ± 14.38 years (male to female

Table 1 Comparison of the visual acuity of affected eyes between two groups of patients in the acute phase recovery ($\bar{x}\pm s$)

Group	Eyes (n)	Age (years)	Mean visual acuity of affected eyes	F value	P value
Acute phase	159	44.84±15.21	0.53±0.33	13.122	0.00
Recovery phase	221	44.14±15.46	0.73±0.28		

ratio 0.92:1.00). There were 127 patients (44.99%) with bilateral disease and 136 cases (51.71%) of monocular disease. The mean visual acuity of the affected eye at the time of initial consultation was 0.63 ± 0.31 and that of the healthy eye was 0.77 ± 0.29 . There were a total of 101 cases (38.4%) of total uveitis, 85 cases (32.3%) of anterior uveitis, 75 cases (28.5%) of posterior uveitis, and 2 cases (8%) of intermediate uveitis. There were 196 cases (74.5%) of primary uveitis, 67 cases (25.5%) of recurrent uveitis; 108 cases (41.4%) of acute uveitis and 155 cases (58.9%) of recovered uveitis. There were 132 cases (50.2%) of topical treatment combined with oral glucocorticoids, 28 cases (10.6%) of immunosuppressive treatment, and 15 cases (5.7%) of treatment with biological agents.

Etiological analysis

According to the histories, clinical manifestations and laboratory findings, there were 105 patients (39.9%) with idiopathic uveitis; 158 patients (60.1%) with an identified etiology or an underlying systemic disease, including 39 cases (14.8%) of Vogt-Koyanagi-Harada disease, 31 cases (11.8%) of rheumatoid-associated uveitis, 20 cases of leukoaraiosis (7.6%), 15 cases of HLA-B27 positive uveitis without systemic disease (5.7%), 15 cases of tuberculosis-associated uveitis (5.7%), 12 cases of combined ankylosing spondylitis (4.6%), 11 cases of juvenile arthritis combined with uveitis (4.2%), 9 cases of viral uveitis (3.4%), 5 cases of Fuchs syndrome (1.9%), and 1 case of SAHPO syndrome (synovitis, acne, pustulosis, bone hypertrophy and osteomyelitis).

Complications and visual impairment

Various ocular complications occurred in 67 cases (25.5%), including macular cystoid edema in 43 cases (16.3%), incomplete posterior iris adhesions in 29 cases (11.0%), secondary glaucoma in 28 cases (10.6%), and concomitant cataracts in 25 cases (9.5%). Adverse reactions associated with oral glucocorticoids occurred in 71 (27.0%) patients, and included gastric discomfort in 29 (11.0%) patients,

facial, chest and back rash in 19 (7.2%) patients, weight gain in 18 (6.8%) patients, bone and joint discomfort in 18 (6.8%) patients, mood effects and insomnia in 8 (3.0%) patients, and fatigue in 5 (1.9%) patients. Mild visual impairment (corrected visual acuity <0.5) was noted in 143 eyes (36.7%), moderate and severe visual impairment (<0.3) was seen in 84 eyes (21.5%), and blinding (<0.05) was seen in 12 eyes (3.1%).

Comparison of the visual acuity in acute, convalescent, primary and recurrent patients

The corrected visual acuity of the patients was 0.53 ± 0.33 in the acute phase, and 0.73 ± 0.28 in the recovery phase, which was statistically significant in both groups ($F=13.122$, $P<0.05$) (Table 1). The corrected visual acuity at the last follow-up was 0.74 ± 0.27 in those patients with initial disease, and 0.62 ± 0.32 in those patients with a recurrence of uveitis, and the difference was statistically significant between the two groups ($F=9.255$, $P<0.05$). There was a statistically significant difference in the presence of ocular complications between patients with an initial onset of uveitis and those with a recurrence of uveitis ($F=59.51$, $P<0.05$); there were no statistically significant differences between the visual acuities in the healthy eyes, the IOP in the affected eyes and the IOP in the healthy eyes ($P>0.05$) (Table 2). There was a statistically significant difference between the corrected visual acuity (0.58 ± 0.24) in patients with idiopathic uveitis and the visual acuity (0.70 ± 0.32) in patients with uveitis associated with other diseases ($F=6.825$, $P=0.01$).

Comparison of the visual acuity and IOP between patients with different types of uveitis

The differences in visual acuity between the affected and healthy eyes in the three groups of patients with total uveitis, anterior uveitis and posterior uveitis were statistically significant ($P<0.05$). There was no statistically significant difference in the IOPs between the affected and healthy eyes ($P>0.05$, Table 3).

Table 2 Comparison of the visual acuity of affected eyes between first-time and recurrent patients ($\bar{x}\pm s$)

Group	Visual acuity of affected eye	Visual acuity of healthy eye	Pressure in the affected eye	Pressure in the healthy eye	With or without ocular complications
Initial group (n=298)	0.74±0.27	0.70±0.29	14.17±3.84	14.73±3.67	0.15±0.36
Recurrent group (n=92)	0.62±0.32	0.78±0.29	14.97±4.14	14.32±3.37	0.32±0.47
F value	9.255	0.019	1.065	1.807	59.513
P value	0.003	0.891	0.303	0.182	0.000

Table 3 Comparison of the visual acuity and IOP between three groups of patients

Group	Panuveitis (n=99)	Anterior uveitis (n=58)	Posterior uveitis (n=71)	F value	P value
Visual acuity in the affected eye	0.57±0.33	0.73±0.29	0.67±0.29	6.663	0.01
Visual acuity in the healthy eye	0.68±0.30	0.80±0.25	0.65±0.34	3.454	0.035
IOP in the affected eye	14.70±3.79	14.76±4.00	14.06±3.65	0.687	0.504
IOP in the healthy eye	14.09±3.78	15.29±3.49	13.87±3.34	1.936	0.149

IOP, intraocular pressure.

Results of correlation analysis

There was a correlation between the visual acuity of the affected eye with the presence of vitreous inflammatory cells ($r=0.174$, $P=0.005$).

Discussion

Uveitis is a group of diseases, with an estimated annual incidence of 38–715 per 100,000 people in developed countries (1). In Swiss, Hoogewoud *et al.* in the past 20 years (between 1 January 2000 and 31 December 2019) found that the incidence of pediatric uveitis is 11% (317/2,468) (11). The disease mainly invades the uveal tissue and causes an intraocular inflammatory response that can cause severe visual impairment. Uveitis accounts for 10–15% of the legally blind patients in the USA and up to 15% of the legally blind patients in other countries around the world (12–14). In this study, the incidence of mild visual impairment was 36.7%, moderate and severe visual impairment reached 21.5%, and the blinding rate was 3.1%. The comparison of the visual acuities of the affected eyes and the healthy eyes among three groups (total uveitis, anterior uveitis and posterior uveitis) was statistically significant, and the visual acuities of the affected eyes and the healthy eyes in patients with anterior uveitis were better than those of patients with posterior and total uveitis. The visual acuity of patients with recovered uveitis

was better than that of patients with acute uveitis, patients with primary uveitis were better than those with recurrent uveitis, and there was a correlation between the visual acuity of the affected eye and the presence of ocular complications, indicating the severity of the disease, the degree of inflammation, and those ocular complications most likely to damage the eye organs such as iris, lens, macula, optic nerve and intraocular pressure and affect visual acuity.

Diagnosing the etiology of uveitis is crucial in determining the treatment and prognosis, but no clear cause is found in approximately 28–45% of cases (14,15). Statistically, idiopathic uveitis accounts for 20–40% of cases and infectious uveitis accounts for 30–50% of cases. However, in developed countries, infectious uveitis accounts for approximately 20%, and the most common cause is herpesvirus infection (16). Sharma *et al.* (17) found that uveitis is associated with systemic diseases. Nelson *et al.* (18) reported that a specific etiological diagnosis was made in around 61% of patients, and in this study, the etiology was identified or combined with systemic diseases in 60.1% of the patients. It has been reported in the literature that rheumatic diseases predispose patients to the development of uveitis and damage to ocular tissues, and other diseases, such as Behcet's disease, syphilis, serosanguinous spondyloarthritis and psoriatic diseases, can also lead to inflammatory responses in the uvea (19). Grumet *et al.* (20) found that the most common systemic diseases associated with uveitis

included spondyloarthritis and HLA-B27-associated uveitis, tuberculosis, and concurrent tuberculosis and herpesvirus infectious uveitis. These five types of uveitis accounted for 70% of all patients, followed by Behçet's disease and syphilis with incidences of 4.2% and 1.7%, respectively. In a study by Gogia *et al.* (21), tuberculosis of the lung was found in 75% of the patients with tuberculous uveitis, anterior uveitis was found in 48.9% of the patients with tuberculous uveitis, posterior uveitis was found in 25.5% of the patients, total uveitis was found in 10.6% of the patients and intermediate uveitis was found in 10.6% of the patients. Multifocal chorioretinitis was the most common type of posterior uveitis. In this study, uveitis was present with systemic disease in 158 cases (60.1%), including rheumatoid-associated uveitis in 11.8% of patients, leukoarthritis in 7.6% of patients, HLA-B27 positive and tuberculosis-associated uveitis without systemic disease in 5.7% each of patients, combined with ankylosing spondylitis in 4.6% of patients, juvenile arthritis combined with uveitis in 4.2%, and 3.4% of viral uveitis.

These findings suggest that patients with uveitis should be actively tested for different etiologies, and that the combination of etiologic and symptomatic treatment results in a faster recovery and better outcomes. Other studies have shown that stress and lack of sleep may contribute to the recurrence of anterior uveitis, while exercise, smoking, and alcohol consumption are not associated with recurrence (22). Other researchers have found that air pollution leads to increased levels of inflammatory cytokines and exacerbates the autoimmune inflammatory response (23).

For the treatment of uveitis, topical and systemic administration of glucocorticoids can control the inflammatory response, especially in the early stages of inflammation when rapid control of the disease is essential, and because long-term usage of glucocorticoids can cause serious side effects, patients with recalcitrant uveitis often need to be treated with a combination of immunomodulatory agents (24). Guidelines for the treatment of uveitis include glucocorticoids as first-line therapy, immunomodulatory drugs such as cyclosporine A, methotrexate, azathioprine, and Mycophenolate Mofetil as second-line therapy, and biological agents [tumor necrosis factor- α antagonists (TNF- α) or interferon- α] as third-line therapy (24,25). Neti *et al.* (22) found that slow-release glucocorticoid injections were rapidly effective in improving visual acuity, with 86% improvement in visual acuity, 27% improvement in pain and 26% improvement in vitreous inflammatory clouding. Posarelli *et al.* (26) found

that systemic steroids were used in 42.86% of the patients with uveitis, and the most common ocular complications were cataracts and an increased IOP, but there was no statistical correlation with systemic steroid application. Pavesio *et al.* (27) found that the use of 0.2 $\mu\text{g}/\text{day}$ fluocinolone acetate implant to prevent the inflammation of posterior non-infectious uveitis reduced the recurrence and need for adjuvant medication, and improved vision, providing greater protection against ocular inflammation than a reactive approach using standard of care. It is more suitable for patients with uveitis recurrence ≥ 2 times a year who need systemic corticosteroids or immunosuppressive therapy. Control rates of 52% for uveitis after 12 months of cyclosporine treatment, 60–76% for azathioprine and methotrexate, 69% for tacrolimus, and 79% for adalimumab have been previously reported; anti-TNF- α agents are particularly effective in patients with idiopathic uveitis without systemic inflammatory diseases (28). Suhler reported that for patients receiving subcutaneous adalimumab 40 mg every other week, quiescence increased from 34% (122/364) at week 0 to 85% (153/180) at week 150 and corticosteroid use was reduced (29). In addition, anti-TNF- α agents can treat juvenile rheumatoid-associated uveitis, control the acute phase inflammatory response and disease severity, and have good efficacy for macular edema secondary to uveitis (30). Silvestri *et al.* found that adalimumab not only reduced macular edema in patients with uveitis but also controlled the active inflammatory response in systemic diseases (31). Puyade *et al.* performed autologous hematopoietic stem cell transplantation for Behçet's disease (BD) and reported an acceptable safety profile for a feasible and relatively effective procedure in severe and conventional treatment-resistant cases of BD that has the potential to stabilize BD in patients with life-threatening involvement (32). In our study, different treatment regimens were selected according to the severity of the patients' disease and systemic conditions, and included topical treatments combined with oral hormone therapy in 132 cases (50.2%), supplemented with immunosuppressant cyclosporine A in 28 cases (10.6%), and combined with adalimumab in 15 cases (5.7%). We found a correlation between the visual acuity of the affected eye, the presence of ocular complications, and recovery. The visual acuity in idiopathic uveitis was statistically significant compared with the visual acuity in other types of disease-associated uveitis.

Therefore, the key aim of treatment is to control the degree of inflammation and prevent irreversible destruction

of the ocular structures and subsequent visual damage. In conclusion, because the etiologies of uveitis are complex, the inflammatory response is variable, and untimely treatment can cause serious visual impairment, every ophthalmologist is responsible for improving treatment techniques, making early and correct judgments about the history and symptoms, giving patients the best treatment options, shortening the course of the disease to reduce pain, and restoring the visual function as soon as possible. At the same time, ophthalmologists, in conjunction with internists, should conduct relevant laboratory tests to identify the cause of the disease, and joint symptomatic treatment improves the outcomes of uveitis. In addition, health education guidance must be given to patients with systemic diseases susceptible to uveitis, and early treatment is given in case of ocular discomfort to avoid further damage to visual function due to disease recurrence.

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Footnote

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