

# An Update-Uveitis in Children

## Introduction

Uveitis is diagnosed more commonly in adults than in children. In children, the difficulty of an early diagnosis may worsen the visual prognosis. The different incidence of the presumed or defined etiologies in the various ages is probably responsible for the better classification of uveitis in childhood. Uveitis in children has a relatively severe course. Prompt diagnosis and treatment can minimize the risk of long-term vision loss. The main problems in detection of intraocular inflammation in children may arise due to inability of children to clearly explain their ocular complaints, the absence of symptoms in certain diseases, e.g., anterior uveitis associated with juvenile rheumatoid arthritis (JRA), and the development of amblyopia if the vision is impaired.

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## Incidence

Uveitis is the third leading cause of blindness in America, and 5% to 10% of the cases occur in children under the age of 16. Several studies have shown that children constitute about 5–10% of all new uveitis patients. In pediatric uveitis, anterior uveitis accounts for 30–40%, posterior uveitis 40–50%, intermediate uveitis 10–20% and panuveitis 5–10 %.<sup>(1–8)</sup> Patients between the ages of 0 to 18 years fall under the category of pediatric uveitis. Uveitis occurring in this age group has been reported at a much lower incidence than in adults<sup>(9, 10, 11)</sup>. Most uveitis surveys have reported either an equal gender distribution or a slight female preponderance<sup>(12)</sup>. South India study has reported a slightly higher incidence in males<sup>(13)</sup>. However, the reported percentage of children affected varies widely, ranging from 2.2–33.1% of all patients with uveitis. In a large study from Israel, anterior uveitis accounted for 13.4% of all cases of uveitis affecting children and adolescents. Acute episodes of inflammation may be self-limited and benign or may cause anterior or posterior synechiae, with secondary glaucoma. Chronic anterior uveitis additionally may cause band keratopathy, cataract, spillover anterior vitritis, cystoid macular edema, glaucoma and phthisis.

**Race:** Sarcoidosis affects African Americans about 10 times more often than whites.

**Sex:** AS is 2–3 times more common in males than in females. Reactive arthritis is 5 times more common in males than in females. Sarcoidosis is slightly more common in females than in males. Oligoarthritis JIA is more common in females than in males, with a female-to-male ratio of 3–4:1.

**Age:** Most children with oligoarthritis JIA are younger than 4 years, while children with RF-negative polyarthritis JIA are older. Enthesitis-related arthritis typically affects older boys<sup>(14, 15)</sup>. Mean age of onset of AS is about 10 years and 10–11 years in psoriatic arthritis.

## History

**Aim:** The main objective in taking the history in children is to narrow the differential

diagnosis, to optimize laboratory testing and to direct appropriate referrals. The parents and the child should be asked about the presence of arthritis, rashes or other skin diseases, gastrointestinal disease or pulmonary conditions. In adult patients with uveitis, a complete examination of the eye and ocular adnexa is required. In uncooperative patients, examination under general anesthesia is required.

- **Skin:** Erythema nodosum is common in sarcoidosis. Blepharitis and blepharoconjunctivitis is seen in herpes simplex virus infection.
- **Lacrimal gland** may be enlarged in sarcoidosis and other infiltrative conditions.
- **Band keratopathy** is seen in JIA-associated uveitis; it may be quite subtle and limited to the limbal areas of the 3-o'clock and 9-o'clock meridians.
- **Geographic or stellate keratitis** suggesting herpes infection.
- **Mutton-fat keratic precipitates (KP)** may be present in granulomatous conditions, but smaller KP occurs in JIA-associated and HLA-B27-associated uveitis.
- **Iris examination** for Koeppe and Busacca nodules, which is seen in granulomatous uveitis.
- **Pseudohypopyon** may indicate leukemia, retinoblastoma and JXG.
- **Vitreous examination** is done for spillover inflammation and exclude intermediate uveitis and pars planitis.
- **Arthritis and joint tenderness** suggest JIA or spondyloarthritis; limited torso flexion occurs in AS; and the development of a new heart murmur along with fever and rash may suggest Kawasaki disease.

## Causes of Uveitis

The cause of uveitis varies which depends upon ecological, racial and socioeconomic variations of the population studied. When examining the causes of uveitis, a marked variability in the incidence and prevalence of the different entities has been observed<sup>(16, 17)</sup>. Aetiologically, the cause of uveitis in children can be classified broadly as infectious and noninfectious. Noninfectious causes of childhood anterior uveitis are more common. The strongest association has been found with JIA. Most cases occur in association with JIA and the spondyloarthropathies. In

children, juvenile idiopathic arthritis (JIA) has been reported as the accompanying systemic manifestation in 81% of children with uveitis and in 95% of children with anterior uveitis.<sup>(18)</sup> Uveitis can occur in 4 of the 7 categories of JIA, including oligoarthritis, rheumatoid factor (RF)-negative poly-arthritis, enthesitis-related arthritis, and psoriatic arthritis. These different incidences of the most prevalent causes of uveitis in children have been attributed to the changing patterns of uveitis.<sup>(19,20)</sup> Spondyloarthropathies (eg, AS, psoriatic arthritis, reactive arthritis, inflammatory bowel disease) also are associated strongly with non-granulomatous anterior uveitis. In one study, infectious uveitis was more common in children, where the most common cause was pediatric parasitic anterior uveitis (29.6%), followed by endophthalmitis (8%), Leptospirosis (5.5%) and toxoplasmosis (4.7%).

## Classification of Uveitis

The uveitis is classified according to the anatomical site of the major inflammatory manifestations and the most probable etiological factors. After 2005, the SUN (Standardized Uveitis Nomenclature) criteria are used to characterize the patients with uveitis. Anatomic location (Anterior, intermediate, posterior, and panuveitis) and characteristics such as- Laterality, onset, duration and course of the disease was taken into consideration.

## Clinical Course Juvenile inflammatory arthritis (JIA) associated uveitis:

JIA refers to arthritis of unknown cause which commonly begins at 2–4 years of age. It is reported to be more common in girls. In majority of cases, the arthritis is diagnosed before the uveitis. The highest risk of developing uveitis occurs within 2 years of diagnosis of JIA and the risk declines greatly 8 years later. Oligoarthritis is the most common type of JIA. Oligoarthritis affects 4 or fewer joints and typically occurs in young girls. Uveitis most often accompanies this form of

the disease and is seen in about 10-30% of patients. Antinuclear antibodies are common in these children. Uveitis occurs in up to 10% of children with RF-negative polyarthritis JIA. Enthesitis-related arthritis affects the attachments of ligaments and tendons to the bone which typically affects older boys. It is often unilateral with a sudden onset. Approximately 10% of children with psoriatic arthritis develop uveitis. In these children, the uveitis is usually chronic and asymptomatic. The ocular manifestations can lead to slow damage over about 4-8 years, if undiagnosed and untreated. The severity of the arthritis is not related to the severity of the uveitis. Typically, the uveitis in eyes of children with JIA-associated uveitis often occurs in a 'white eye'. In the absence of redness and visible inflammation, the reporting is usually delayed. In addition, as affected children are often young, they may not notice or tell changes to their vision. The children with JIA need to be examined periodically. Poorly controlled uveitis related to JIA may progress to band keratopathy, hypo tony, and phthisis.

### Reactive Arthritis:

The classic description of reactive arthritis is that of a triad of urethritis, conjunctivitis, and arthritis. The attacks typically last from 2-3 months. In children, disease onset may occur following enteritis due to Salmonella, Shigella, Yersinia, or Campylobacter species. Antecedent chlamydial urethritis is seen in adult cases. Acute or chronic nongranulomatous anterior uveitis occurs in reactive arthritis in approx 30% of cases.

### Ankylosing Spondylitis:

Average age of onset is 11.5 years, and males are 3 times more affected than females. AS is characterized by painful stiffening of the back caused by sacroiliitis and lumbosacral spondylitis. Lower back pain is the usual presenting symptom, although some patients have peripheral arthritis.

### Sarcoidosis:

It is an important cause of panuveitis but may present as an isolated non-granulomatous anterior uveitis. Uveitis associated with sarcoidosis is significantly less common in

children compared to JIA-related causes and uveitis related to spondyloarthritis. Children who have findings suggestive of sarcoidosis should undergo a complete examination by a pediatrician. The examination should include a thorough evaluation of the lungs and a determination of serum and urine calcium levels.

### Kawasaki Disease:

Kawasaki disease is a systemic disease of unknown cause affecting children and adolescents. Its major features are protracted fever, cervical lymph node swelling, strawberry tongue (prominence of tongue papillae), palmar erythema, erythematous rash, and bilateral conjunctival injection.

**Infectious causes of uveitis:** Rathinam et al have reported that infectious uveitis is more common in children. The most common cause was pediatric parasitic anterior uveitis (29.6%) followed by endophthalmitis (8%), Leptospiral uveitis (10.5%), tuberculosis (5.9%) and herpetic anterior uveitis (4.5%)<sup>(12)</sup>.

### Toxoplasma-related Uveitis:

It is caused by *Toxoplasma gondii*, which is carried by cats and is shed in their faeces; it is caught by eating substances directly contaminated by these faeces, or by eating undercooked infected meat such as pork, beef, lamb and chicken. If a mother becomes infected during pregnancy, the unborn child can get the infection. Toxoplasma Infection is common in childhood and the eyes are often affected. Most of the times, the infection leads to small scars at the posterior pole of the fundus without having effect on vision and are only detected on routine examination. However, these Toxoplasma scars can reactivate many years later, causing visual problems.

### Toxocara-Related Uveitis:

It occurs in children due to infection with *Toxocara canis*, which is carried by dogs and cats and is shed in their faeces; it is caught by subsequent food contamination. Although infection is common in children, the ocular involvement is rare. Infection is most common at 2-3 years of age. It is more common in boys

than girls. The infection causes a granuloma in the eye which can sometimes be seen as a 'white reflex'.

### Intermediate Uveitis/ Pars Planitis:

It generally begins in one eye, but becomes bilateral. It commonly causes floaters and blurring of vision. The other common infectious causes are due to viral infections of the eye – Herpes simplex, Herpes zoster and following systemic viral syndromes like mumps, measles, varicella, mononucleosis. Uveitis associated with herpes simplex often is accompanied by keratitis. Uveitis in children with herpes zoster usually occurs when there is associated immune suppression, eg in AIDS.

### Management Medical Care

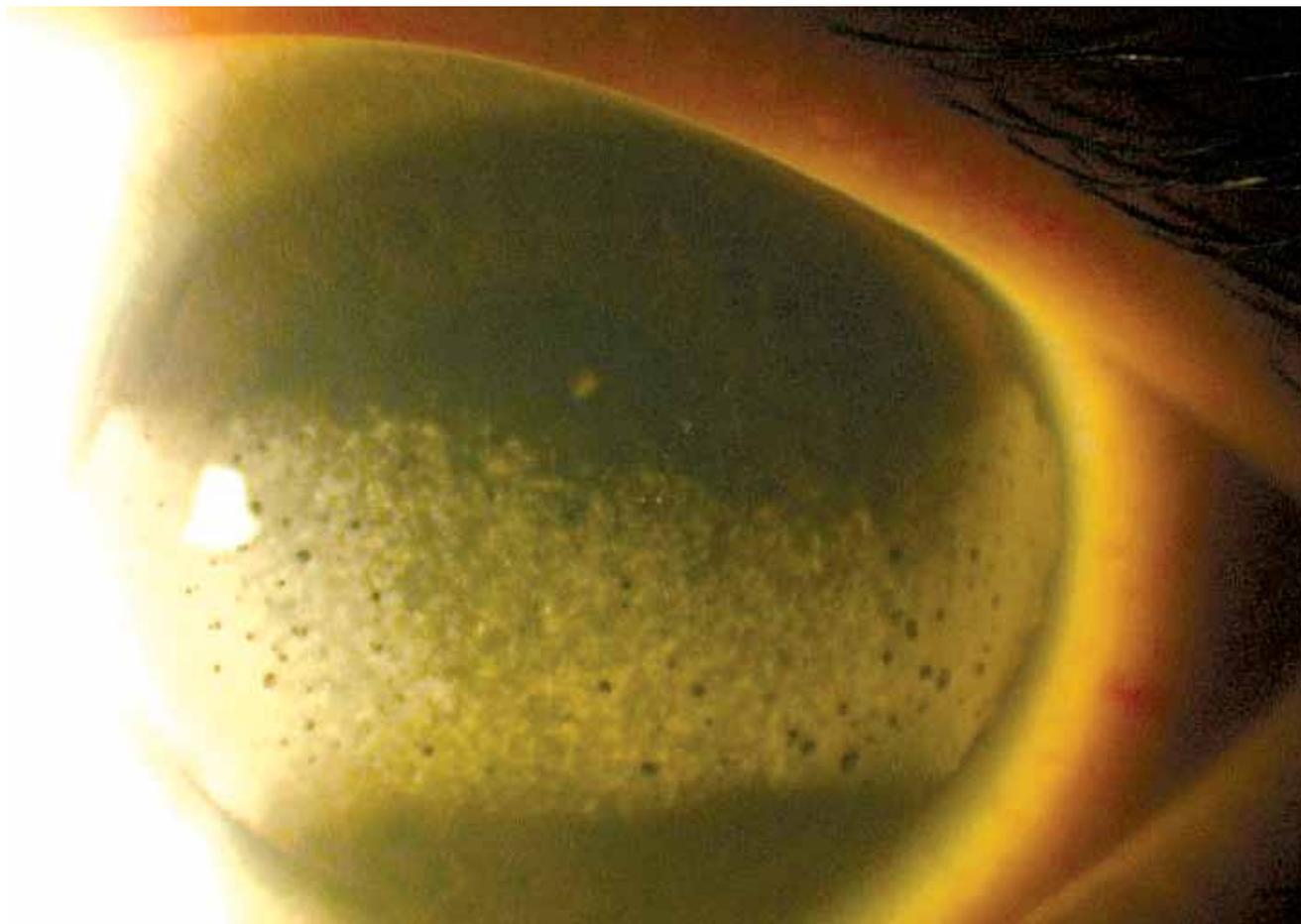
The diagnosis and management of chronic pediatric uveitis can be particularly challenging, with an estimated 25-33% of childhood uveitis cases resulting in severe, life-long visual disability. Knowledge of the ocular complications of chronic pediatric uveitis can help to customize efficacious therapeutic regimens for each patient, maximize the visual potential and minimize complications of these diseases. The primary medications used in treating anterior uveitis in children are corticosteroids, topical cycloplegics, and, in certain cases of JIA-associated uveitis, methotrexate<sup>(21, 22)</sup>.

### Surgical Care

Surgery is required to treat the complications of severe or chronic inflammation. For example, in JIA-associated uveitis, cataract often develops and the eye should be quiet for at least 3 months prior to surgery. Severe band keratopathy, as seen in JIA, may require treatment with Ca EDTA chelation. Development of glaucoma may require trabeculectomy or placement of a drainage implant.

### Differential Diagnosis

- 1) Juvenile Xanthogranuloma
- 2) Leukemia



## Investigations

If JIA is suspected, an antinuclear antibody test is to determine the risk of recurrent and severe disease. In patients of AS, reactive arthritis, or inflammatory bowel disease, HLA-B27 haplotype is done. Sacroiliac joint films may demonstrate evidence of joint involvement in AS and reactive arthritis. Sarcoid uveitis is investigated with determination of the angiotensin-converting enzyme (ACE) level, with or without serum lysozyme testing, chest roentgenograms, and gallium scanning. Definitive diagnosis requires histopathology demonstration of noncaseating granulomatous inflammation, in the absence of another possible cause. If symptoms suggest TINU, urinalysis, serum creatinine, and urine beta-2-microglobulin testing is indicated.

## Follow-up

Follow-up care is on a case-by-case basis and depends on the cause of the uveitis, the

severity of the uveitis, and the medications used in treatment.

The German Uveitis in Children Study Group recommends screening examinations for children with JIA as outlined below.

- Children with JIA and no previous history of uveitis.
- Oligoarthritis, RF-negative polyarthritis, or early childhood psoriatic arthritis: Screening examinations should be conducted at 6-week intervals for 2 years, then every 3 months for the next 5 years.

Children with JIA and a history of uveitis: The intervals of screening examinations should be adjusted based upon the activity and the treatment of the uveitis.

Enthesitis-associated arthritis or late onset psoriatic arthritis: Screening examinations should be conducted every 6 months.

Systemic arthritis or RF-positive polyarthritis: Screening examinations should be conducted every 3 months for 7 years.

## Consultations

Depending on the patient, one or more of the following pediatric subspecialists may assist in the evaluation and treatment of patients:

- Rheumatologist
- Pulmonologist
- Oncologist
- Cardiologist
- Gastroenterologist
- Neurologist
- Infectious disease specialist
- Nephrologist

## Complications

Complications of uveitis may include the following:

- Band keratopathy
- Cataract
- Glaucoma
- Hypotony
- Amblyopia
- Synechiae
- Cystoid macular edema
- Phthisis

## References

1. Cunningham ET Jr. Uveitis in Children. *Ocular Immunology and Inflammation* 2000; 8:251-61.
2. Ben Ezra D, Cohen E, Maftzir G. Patterns of intraocular inflammation in children. *Bull Soc Belge Ophthalmol* 2001; 25-38.
3. Perkins ES. Pattern of uveitis in children. *Br J Ophthalmol* 1966; 50:169-85.
4. Tugal-Tutkun I, Havrlikova K, Power WJ, Foster CS. Changing patterns of uveitis in childhood. *Ophthalmology* 1996; 103:375-83.5. Giles CL. Uveitis in childhood-Part I Anterior. *Ann Ophthalmol* 1989; 21:13-19.
6. Giles CL. Uveitis in childhood-Part II Intermediate. *Ann Ophthalmol* 1989; 21:20-22.
7. Giles CL. Uveitis in childhood-Part III Posterior. *Ann Ophthalmol* 1989; 21:23-28.
8. Kanski JJ, Shun Shin GA. Systemic uveitis syndromes in childhood: An analysis of 340 cases. *Ophthalmology* 1984; 91:1247- 52.
9. Biswas J, Narain S, Das D, Ganesh SK. Pattern of uveitis in referral uveitis clinic in India. *Int Ophthalmol* 1996; 20:223-8.
10. Pivetti-Pezzi P. Uveitis in children. *Eur J Ophthalmol* 1996; 6: 293-8
11. Cunningham ET Jr. Uveitis in children. *Ocul Immunol Inflam* 2000; 8:251-61
12. Henderly DE, Genstler AJ, Smith RE, Rao NA. Changing pattern of uveitis. *Am J Ophthalmol* 1987; 103:131-6.
13. Rathinam SR, Namperumalsamy P. Global variation and pattern changes in epidemiology of uveitis. *Indian J Ophthalmol* 2007; 55:173-83.
14. BenEzra D, Cohen E, Maftzir G. Uveitis in children and adolescents. *Br J Ophthalmol*. Apr 2005; 89(4):444-8.
15. Zierhut M, Michels H, Stubiger N, Besch D, Deuter C, Heiligenhaus A. Uveitis in children. *Int Ophthalmol Clin*. 2005; 45(2):135-56.
16. Rathinam SR, Usha KR, Rao NA. Presumed Trematode granulomas of anterior chamber: A newly recognized cause of uveitis in children from South India. *Am J Ophthalmol* 2002; 133:773-9.
17. Rathinam SR, Fritsche TR, Srinivasan M, Vijayalakshmi P, Read RW, Gautom R, et al. An outbreak of Trematode-induced granulomas of the conjunctiva. *Ophthalmology* 2001; 108:1223-9.
18. Cunningham ET Jr. Uveitis in children. *Ocul Immunol Inflam* 2000; 8:251-61
19. Pivetti-Pezzi P. Uveitis in children. *Eur J Ophthalmol* 1996;6: 293-8
20. BenEzra D, Cohen E, Maftzir G. Uveitis in children and adolescents. *Br J Ophthalmol* 2005; 89:444-8.
21. Rajaraman RT, Kimura Y, Li S, Haines K, Chu DS. Retrospective case review of pediatric patients with uveitis treated with infliximab. *Ophthalmology*. Feb 2006; 113(2):308-14.
22. Saurenmann RK, Levin AV, Rose JB, Parker S, Rabinovitch T, Tyrrell PN, et al. Tumour necrosis factor alpha inhibitors in the treatment of childhood uveitis. *Rheumatology (Oxford)*. Aug 2006;45(8):982-9.

## About the Author



**Dr Alok Agrawal** graduated from India in 2003. After his undergraduate degree, he did a long-term observer-ship in different eye hospitals in USA. He received his Postgraduate degree in Ophthalmology from India in 2008.

He did his long term fellowship training in Uveitis in 2008 at Sankara Nethralaya, India and later has acquired a wealth of experience in managing patients with a variety of complex ocular inflammatory diseases after doing another International Clinical Fellowship in Ocular Immunology & Inflammation Services from Singapore National Eye Center, Singapore for a year.

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