CHAPTER 5:
UVEITIS IN DIABETES

UVEITIS:defined as the inflammation of uveal tissue of the eye.

Types of uveitis: There are several types of uveitis:

a) Based on the site of inflammation:

Anterior uveitis– It isthe most common form, occurs in very young to middle-aged people. It occurs when the iris and the ciliary body become inflamed, and has been linked to patients suffering from rheumatologic, skin, gastrointestinal, lung and infectious diseases. This type is usually seen in diabetes.

Intermediate uveitis– occurs mostly in children, teenagers and young adults. It occurs when the area behind the ciliary body i.e vitreous becomes inflamed and has been associated with patients suffering from inflammatory bowel disease, sarcoidosis and multiple sclerosis usually.

Posterior– the least common type, occurs when the choroid and the retina at the back of the eye become inflamed.

Panuveitis– when all three major parts of the eye are affected by inflammation.

b) Based on pathology:

Granulomatous uveitis: Granulomatous uveitis is an inflammation of the uveal tract characterized by the formation of granulomas due to infectious or non-infectious causes. It may be associated with a systemic disease and can involve any part of the uveal tract. The systemic diseases can include debilitating and life-threatening conditions for which ocular manifestations may be the first presentation.

Non-granulomatous uveitis: Non-granulomatous uveitis is a type of uveitis that is characterized by acute onset, severe pain, and intense sensitivity to light. The causes of non- granulomatous uveitis include seronegative arthropathy, trauma, Behcet's

syndrome, leptospirosis, sarcoidosis, tuberculosis, and syphilis. Non-granulomatous uveitis typically has an acute onset and shows fine KP (keratic precipitates). Though there are many causes for non-granulomatous uveitis, it is more likely to be idiopathic.

c) **Based on eitiology:**

Traumatic

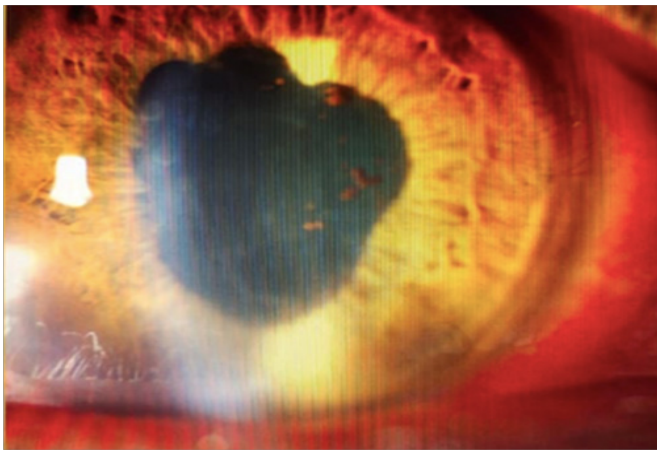
Immunologic

Infectious

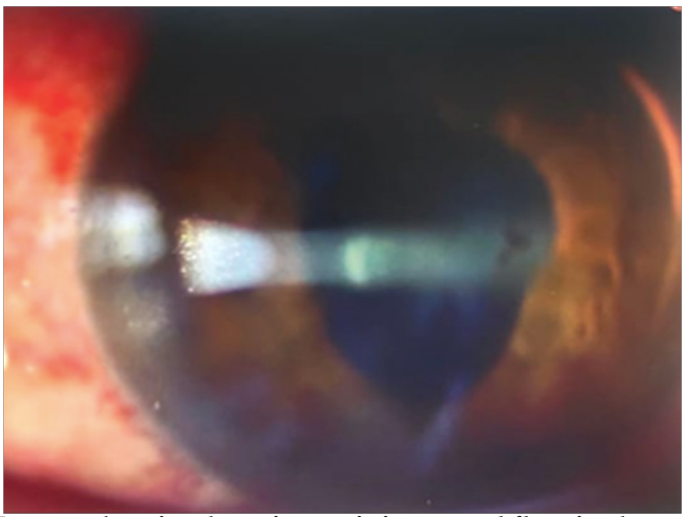
Masquerade

Association of uveitis with diabetes:

Diabetic eye problems are generally caused due to blood vessel and nerve damage that occur due to high sugar levels. Poor diabetes control is known to be a major cause for many diabetic eye diseases including conditions of the iris. Diabetic eye problems of the iris include iritis (anterior uveitis), iris transluminance, and rubeosisiridis. These conditions arise due to uncontrolled diabetes and chronic high blood sugar levels. A variety of conditions cause uveitis which can be a potentially blinding condition. While many cases are idiopathic, it is associated with a number of systemic diseases and infectious agents. It is the fifth commonest cause of blindness in the developed world. The incidence of diabetes mellitus (DM) is increasing rapidly in developed nations. link between diabetic autonomic neuropathy and uveitis has been suggested, and others have found a definite association between DM and uveitis.



a) Image: showing acute anterior uveitis in a diabetic patient



b) Image: showing keratic precipitates and flare in the same patient

Pathology:

A proposed mechanism for the relationship between DM and uveitis is the disruption of the blood-ocular barrier in diabetic patients in both the anterior segment as well as in the posterior segment leading to a higher degree of inflammation,

hence leading to an increased risk of developing acute anterior uveitis(AAU) in anterior segment. Several studies haveshowed that poor glycaemic control can result in a more severe ocular inflammation than good control in diabetic patients. Aqueous flare intensity has also been shown to be significantly elevated in patients with proliferative diabetic retinopathy compared with that in control or patients with non-proliferative retinopathy. Some studies have suggested that poor glycaemic control may be a trigger for recurrence of uveitis of all types as well.

Examination of iris specimens from eyes of patients with diabetes who have undergone iridectomy during cataract surgery has revealed the formation of gaps between the endothelial cells of the iris vessels. These findings suggest that severe disruption of the blood–ocular barrier occurs in conditions of more severe hyperglycaemia, which in turn likely promotes infiltration of inflammatory cells and leakage of protein from the iris vessels.

Interestingly It has also been found that diabetes treatment drugs suppress inflammation in endotoxin-induced uveitis. Kemmochi and colleagues have suggested that diabetes might be one of the contributing factors to the better inflammatory control of uveitis because drugs for diabetes improved carbohydrate metabolism and also decreased ocular inflammation.

Furthermore, Some studies have proposed that several antidiabetic drugs used in clinical practice for patients with diabetes exert anti-inflammatory effects partly as a result of reducing high blood glucose levels. Thus, it is possible that glucose-lowering therapy might also contribute to the reduction of ocular inflammation with anterior uveitis.Thus, it would be reasonable to consider good glycaemic control as an important factor in the prevention of recurrent inflammation. It has been found that uveitis cases associated with decompensated diabetes mellitus were always anterior and had a much worse inflammation compared with diabetes mellitus associated uveitis (DMAU) in patients with well-controlled diabetes.

Patients with DMAU with poorly regulated DM presented a more intense anterior chamber reaction, presence of hypopyon,

fibrin and posterior synechiae, and a worse diabetic retinopathy than patients with DMAU with well-controlled DM. Although all patients in the DMAU with poorly controlled DM usually respond well to topical or periocular steroids within weeks.

Whether the hyperglycemia by itself initiates the inflammation process by inducing ischemia, a break- down of the blood-ocular barrier or modifying the immune response, or makes a different underlying inflammation process worse, is difficult to assess. It is hypothesized that the uncontrolled diabetes by itself can drive inflammation through a seriesof mechanisms that induce a severe anterior chamber inflammation, and thus may be an independent cause of uveitis.

Blood ocular disruption is the main proposed mechanism in association of diabetes and uveitis, but several other hypotheses have been put forward as well. Rothova et al proposed an inflammatory process as they found the absence of retinopathy in more than half of the diabetic patients with uveitis, recurrent episodes, and a good response to local steroids.

Castagna et al found a significant increase in the CD8+ subset, with CD4 + T cells within normal limits, and a decrease in the CD4+/CD8 ratio in all patients with anterior uveitis and type 1 DM, which could be an expression of the unstable lymphocyte equilibrium. Along the same line, Guy et al found an association between iritis and severe symptomatic autonomic neuropathy, suggesting a common pathogenic mechanism where insulin antibodies may cross-react with nerve growth factor, which can accumulate in the iris upon sensory or sympathetic denervation. Finally, the blood-ocular barrier breakdown and/or ocular ischemia from pre-existing DM could be an additional pathogenic pathway.

Diagnosis of uveitis:

Iritis or anterior uveitis occurs more in people with type 1 diabetes and people with other diabetes complications like diabetic neuropathy and diabetic nephropathy. Anterior uveitis or iritis is a condition that causes inflammation of the iris. Though this condition is caused due to infectious diseases, it occurs more in

people with type 1 diabetes due to nonspecific causes.

In order to diagnose iritis or anterior uveitis, it is important to consider the clinical presentation of the patient. Tests to diagnose anterior uveitis include:

- Slit-lamp examination
- B-scan ultrasonography
- Fluorescein angiography
- Optical coherence tomography
- Ultrasound biomicroscopy

Treatment of uveitis:

If the uveitis is infectious, whether viral, bacterial or fungal, we treat with the appropriate antiviral, antibacterial or antifungal medication

Management of anterior uveitis:

Anterior uveitis can generally be managed by medical therapy and requires surgical intervention only if structural complications supervene and those can be either secondary glaucoma or secondary cataract. The general goals of medical management are:

- Relief of pain and photophobia
- Elimination of inflammation
- Prevention of structural complications such as synechiae, secondary cataract and glaucoma
- Preservation or restoration of good visual function.

However, one needs to remember the potential side-effects and long-term iatrogenic complications secondary to the use of steroid therapy. The risk-benefit ratio should be analyzed on a case-to-case basis.

Noninfectious anterior uveitis is treated using the following drugs:

A) Corticosteroids

Corticosteroids are the drug of choice in the treatment of uveitis. Steroids act by modifying and decreasing the inflammatory response in the eye. They act on both cycloxygenase pathways of inflammatory response and inhibit them. Various routes of administration are:topical,periocular and systemic.

Topical drops are the commonest and easiest method with the least side-effects , some topical corticosteroids are :

- Prednisolone acetate 0.125% and 1%
- Betamethasone 1%
- Dexamethasone sodium phosphate 0.1% (also available in 0.05% ointment form)
- Fluorometholone 0.1% and 0.25% (also available in 0.1% ointment form)
- Loteprednol

The choice of topical steroid should be based on the severity of uveitis; in cases with severe AC reaction topical steroid with strong potency such as prednisolone acetate should be preferred whereas in cases with mild anterior uveitis weak topical steroid such as betamethasone or dexamethasone can be applied. In steroid responders one should try and avoid steroid as far as possible and can use topical non-steroidal anti-inflammatory drugs (NSAIDs) like flurbiprofen.

Periocular injection is indicated where maximum concentration of the drug is required for a longer time with minimal side-effects. The drugs which can be considered for periocular injections are dexamethasone or triamcinolone acetonide. Posterior sub-tenon's injection is recommended in intermediate and posterior uveitis.

Systemic corticosteroids are indicated when the anterior uveitis is not responding to topical drugs alone or if the disease is recurrent and bilateral or if there is posterior segment involvement. The guidelines for oral corticosteroids therapy are:

- Use enough, soon enough, often enough, and long enough to secure the desired results.
- Start with high dose and taper according to the clinical response.
- Suppress inflammation till the pathogenic effect ends.
- The dose of steroid should be planned but in accordance to the response of the disease.

B) Mydriatics/cycloplegics:

These are given as supportive measures. They cause paresis of the iris and ciliary muscle and keep the pupils mobile thus preventing the formation of synechiae. These cycloplegic agents are cholinergic antagonists which work by blocking neurotransmission at the receptor site ofthe iris sphincter and ciliary muscle. They serve three purposes in the treatment of anterior uveitis:

- They relieve pain by immobilizing the iris
- They prevent adhesion of the iris to the anterior lens capsule (posterior synechia), which can lead to iris bombe and elevated IOP
- They stabilize the blood-aqueous barrier and help prevent further protein leakage (flare).

Cycloplegic agents useful in treating anterior uveitis are:

- Atropine, 0.5%, 1%, 2%
- Homatropine, 2%, 5%
- Cyclopentolate, 0.5%, 1%, 2%.

Phenylephrine, 2.5%. phenylephrine has neither a cycloplegic nor anti-inflammatory effect and may cause a release of pigment cells into the AC and it is generally not recommended as an initial part of the therapeutic regimen. Although it helps in breaking recalcitrant posterior synechia.

C) Non-steroidal anti-inflammatory drugs

These work by inhibition of arachidonic acid metabolism and include drugs such as indomethacin, flurbiprofen and diclofenac sodium. When used alone,however, their efficacy in treating acute intraocular inflammation has not been established.

D) Immunosuppressive agents

These are used mainly in corticosteroid-resistant cases or as steroid-sparing agents. The immunosuppressives commonly used are methotrexate or azathioprine. One needs to start immunosuppressive in conjunction with the internist.

References

1. Noyes HD. Retinitis in glycosuria. Trans Am Ophthalmol Soc. 1868;1:71–75.

2. Leber T. Ueber das Vorkommen von Iritis und Iridochorioiditisbei Diabetes mellitus und beiNephrititisnebstBemerkungenüber die Wirkung der SalicylsäurebeiinnerenAugenentzündungen. Albr von Græfe's Arch fürOphthalmol. 1885;31(4):183–202. doi:10.1007/BF01693892.

3. Guy RJC, Richards F, Edmonds ME, Watkins PJ. Diabetic autonomic neuropathy and iritis: an association suggesting an immunological cause. Br Med J. 1984. doi:10.1136/ bmj.289.6441.343.

4. Rothova A, Meenken C, Michels RP, Kijlstra A. Uveitis and diabetes mellitus. Am J Ophthalmol. 1988;106:17–20.

5. IDF diabetes atlas. http://www.diabetesatlas.org/. Accessed August 28, 2018.

6. Suttorp-Schulten MS, Rothova A. The possible impact of uveitis in blindness: a literature survey. Br J Ophthalmol. 1996;80:844–848.

7. Oswal KS, Sivaraj RR, Stavrou P, Murray PI. Clinical fea- tures of patients with diabetes mellitus presenting with their first episode of uveitis. OculImmunolInflamm. 2009;17(6):390– 393. doi:10.3109/09273940903200309.

8. http://www.diabetes.org.uk/Documents/Reports/Diabetes_in_the_UK_2010.pdf.

9. Durrani OM, Tehrani NN, Marr JJ, Moradi P, Stavrou P, Murray PI: Degree,

duration and causes of visual loss in uveitis. Br J Ophthalmol 2004, 88:1159–1162.

10. Jabs DA, Nussenblatt RB, Rosenbaum JT: Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol 2005, 140:509–516.

11. Martyn CN, Young RJ, Ewing DJ: Is there a link between iritis and diabetic autonomic neuropathy. Br Med J 1986, 292:294.

12. Murray PI, Russell-Eggitt IM: An unusual presentation of diabetes mellitus. MetabPediatrSystOphthalmol 1991, 14:16–17.

13. Herranz MT, Jimenez-Alonso J, Martin-Armada M, Omar M, Ribera F: Increased prevalence of NIDDM in anterior uveitis. Diabetes Care 1997, 20:1797–1798.