



Vernal Keratoconjunctivitis

WHAT IS IT?

Vernal keratoconjunctivitis (VKC) is a chronic, bilateral, and severe form of allergic and inflammatory conjunctivitis affecting the ocular surface. It is essential to diagnose this condition early and manage it promptly to prevent potentially sight threatening corneal sequelae¹.

WHO DOES IT AFFECT?

The majority of VKC occurs in patients between the ages of 5-25 years old with a typical age of onset before 10 years old, however there have been reports of VKC in infants as well^{1,2}. Recently adult onset VKC has been recognized and appears to have a distinct biological profile³. Males tend to be more affected than females^{1,2}.

People living in warm, dry areas and subtropical climates such as Central and West Africa, the Middle East, South American and Mediterranean regions, and Asian Countries such as Japan, Thailand and India have the highest prevalence. Put simply, the closer to the equator, the higher the incidence^{2,4,5}.

HOW COMMON IS IT ?

Its prevalence is reported to be between 3.2/10,000 population in Western Europe⁵ to 400/10,000 in Central Africa⁴

WHY DOES IT OCCUR?

Even though the exact pathogenic mechanisms of VKC are not completely elucidated, classic immunoglobulin E (IgE) mediated hypersensitivity and T helper cell type 2 (Th2) mediated responses are thought to play a major role in its pathogenesis. VKC may be associated with other atopic manifestations with asthma and allergic rhinitis being the most common concomitant atopic diseases^{6,7}

WHAT ARE THE SYMPTOMS ?

Allergic ocular surface inflammation is mediated by mast cells and typical symptoms in the acute phase are itching, redness, photophobia, lid swelling and conjunctival chemosis (Please see WSPOS consensus statement on Allergic Eye Disease 2023). The most common manifestations of VKC are itchy eyes and photophobia. Other symptoms may include ocular mucoid discharge, tearing, burning, foreign body sensation, ocular pain, and blurred vision. Typically, there is exacerbation of VKC-related symptoms during spring season, though almost a quarter of patients may have a perennial form with recurrences throughout the year, due to responsible allergen or allergens^{1,4,6,8,9}

WHAT ARE THE SIGNS ?

Clinical signs include giant cobblestone-like papillae on the upper tarsal conjunctiva and Trantas dots at limbus of cornea.

Clinical exam shows giant papillae on the upper tarsal conjunctiva in most of the patients with VKC. Other signs include conjunctival and episcleral infection, superficial keratopathy, mucous discharge, Horner-Trantas dots at the corneal limbus, Ptosis from cobblestone papillae and blepharospasm^{1,4,8,9}

Atopic keratoconjunctivitis is often misdiagnosed as VKC. In AKC eyelid skin changes of thickening (eczema) and the double fold of Denier reveal the true diagnosis. AKC is much more chronic than VKC and treatment is often much more prolonged¹⁰.

According to the predominance of signs, VKC has been divided into 3 clinical forms: Tarsal (Palpebral) form - predominantly involving upper tarsal conjunctiva, Limbal form - primarily involving the limbus, showing gelatinous, confluent infiltrates called Horner-Trantas dots and Mixed form. The limbal form may involve the cornea, showing superficial peripheral neovascularization. If chronic and untreated, the limbal stem cell deficiency can lead to conjunctivalization^{1,12}. The tarsal form with giant papillae may be associated with punctate corneal epitheliopathy, shield ulcers, subepithelial scarring, and plaque formation. Some of these can result in severe visual impairment if not diagnosed and treated early.

The severity of the disease has been graded in the Bonini Scale; 1 - mild, 2 - moderate, 3 - severe and 4 - very severe¹⁰.

WHOW DOES IT AFFECT PATIENTS' QUALITY OF LIFE?

Studies have shown that VKC affects the common daily living experience of children, causing problems when they go swimming, play outside, practice sports and meet friends¹³⁻¹⁶.

Additionally, studies have shown that when the quality of life scores of children with VKC are compared to those of children with other medical conditions, they are comparable or even worse than those of children who are hospitalized.

Moreover, the clinical grade of the ocular disease does NOT correlate with the quality of life score. Put simply, a child may have mild ocular disease but their quality of life is severely affected. Some studies showed this affection to extend to the quality of sleep of these children and their parents. This may include sleep onset delay, duration of sleep, disordered sleep breathing, and sleepiness during the day. The quality of life has been proven to show improvement with better control and treatment for these children and their families¹³⁻¹⁶.

The clinician needs to establish the effect of the disease on the patient's quality of life.

HOW DO WE TREAT VKC^{1,4,17?}

Firstly, the correct diagnosis must be made. Recognizing AKC versus VKC changes the counselling and the systemic approach to the disease.

Once the diagnosis is confirmed, it is important to reiterate to the family that management of VKC is long-term and requires frequent follow-up. This is crucial in successful management.

FIRST STEP:

Assess the clinical severity and ask the patient and his/her parents how the patient's quality of life is affected. Photographic documentation of the condition at presentation and at different stages of therapy is common and beneficial in disease monitoring. Suggested questions to assess affect on quality of life are:

Does your child have problems going out on a sunny day?

Does your child have problems going swimming?

Does your child have problems meeting / going out with friends?

Does your child have problems practicing sports?

A mild clinical grade, but a severe effect on quality of life changes the treatment algorithm.

SECOND STEP:

- Allergen avoidance: this is very important. If possible, an allergist or immunologist should be involved when a child has VKC, This is because, if a single allergen is identified, desensitization by immunotherapy with the allergist may be useful.
- Ocular Hygiene with regular ocular washing.
- Encourage hand hygiene.
- Cool compresses with a cloth that must be washed routinely to prevent the cloth harboring allergens.
- Cool showers may offer a better alternative for some children.
- If the child has a favorite cuddly toy, it may be carrying allergens, so consider putting it in a freezer once a week or washing it if possible.
- Changing clothes before sleeping during allergy season (sleeping in pollen saturated clothes may increase the exposure and spectrum of disease).
- Frequent washing of linens.
- Minimizing sharing of furniture with pets.
- Avoidance of eye rubbing to prevent complications like keratoconus.

THIRD STEP:

Treat any underlying conditions such as blepharitis, meibomian gland dysfunction and dry eye syndrome: reducing the inflammatory load helps treat the symptoms and signs of VKC.

FOURTH STEP: TOPICAL AND SYSTEMIC THERAPY

TOPICAL EYE DROPS:

Whenever possible, **try to use preservative free eyedrops.**

Ocular lubricants may help keep the eye comfortable.

Anti-Allergy Drops

Topical antihistamine or a mast cell stabilizer may work in mild cases. Mast-cell stabilizers have a loading period to reach their full therapeutic effect. If seasonal recurrences are common, it is recommended to start mast-cell stabilizers prior to the onset of season and continue them throughout the season.

A topical **dual-acting mast cell stabilizer and antihistamine** may be effective early on, in mild to moderate cases. Dual-acting agents such as olopatadine, azelastine hydrochloride, epinastine, and ketotifen fumarate, act by stabilizing the mast cells by inhibiting mast cell degranulation and additionally inhibit leukocyte activity and dampen mediator release from mast cells, basophils, eosinophils, and neutrophils. They also competitively and irreversibly block histamine receptors in the conjunctiva and eyelids.

Interestingly a meta-analysis of all the different types of anti-allergy drops mentioned above showed that no one drop was superior to any other but the use of at least one was helpful in both allergic eye disease and VKC¹⁸.

Topical steroids

Short term, high pulse dose of topical corticosteroids with quick tapering, is often necessary in patients with VKC who fail to respond to 2-3 weeks of dual-acting mast cell stabilizers and antihistamine eyedrops. Topical steroids should be considered rescue therapy and NOT maintenance therapy. In severe cases of VKC, prednisolone acetate is typically most effective in alleviating the acute symptoms, but also has the greatest risk of raising intraocular pressure (IOP). In cases where steroid response has been observed previously, topical "soft" corticosteroids such as fluorometholone and loteprednol etabonate have less risk of raising IOP and can be used for 2-3 weeks under close supervision to allow for dual-acting drugs to start working.

Unsupervised chronic use of topical steroids can result in visual loss which may be irreversible e.g., glaucoma¹⁹ and optic nerve damage¹⁹ or reversible e.g., cataract, or both⁷.

Calcineurin Inhibitors

Calcineurin (CaN), a calcium and calmodulin dependent serine / threonine protein phosphatase, activates the T cells of the immune system and can be blocked by drugs. The two topically available calcineurin inhibitors as eye preparations are tacrolimus and cyclosporine. Traditionally they are thought of as drops to be used as a last resort, but two recent publications^{4,17} have shown that their use early in the treatment algorithm of VKC improves both clinical signs and quality of life with a reduced need for rescue therapy with topical steroids. Topical calcineurin inhibitors do not cause secondary glaucoma or cataracts.

Topical ocular Cyclosporine-A in concentrations of 0.05-2% has been shown to decrease inflammatory cytokines. A newer Cyclosporine ophthalmic cationic emulsion 0.1% technology enables rapid spread, maximization of contact, prolonged exposure, and near doubling of concentration of cyclosporine in the cornea, thereby inhibiting chronic inflammation in VKC²⁰. This specific preparation has been FDA and EMEA approved for the use in VKC in children.

Topical ocular tacrolimus is effective at concentrations ranging from 0.003% to 0.1%²¹.

Lack of availability of the topical ocular calcineurin inhibitors in some parts of the world necessitates the use of compounding pharmacies to obtain the eyedrops.

The early use of calcineurin inhibitors prevents the development of severe complications.

SYSTEMIC THERAPY:

Oral anti-histamine e.g., cetirizine or loratadine, may be helpful in treating VKC and especially AKC. It is especially helpful if there is concurrent rhinitis⁷.

Systemic immunotherapy should be considered under the supervision of an allergist or immunologist in recalcitrant cases²².

In severe cases oral steroids have been used²³ but there are no randomized control trials for any systemic therapies for VKC²⁴. There are reports of the use of systemic cyclosporine A and tacrolimus in cases of severe and recalcitrant atopic keratoconjunctivitis with ocular involvement^{25,26,27}.

Recently, attention has turned to the use of Omalizumab^{28,29} a monoclonal chimeric anti-IgE antibody that binds to the Ce3 domain of free circulating IgE, inactivating immune complexes. It has been used in patients with eczema and asthma and so more likely to have been AKC related ocular disease. If a patient has VKC with severe asthma a pediatrician must be involved as such patients may require systemic steroids.

FIFTH STEP:

SURGICAL MANAGEMENT OF VKC COMPLICATIONS:

Giant papillae may require supratarsal steroid injection with short and long acting steroids. In rare cases, giant papillae may be intractant and may require surgical removal and amniotic membrane grafting.

A shield ulcer with no plaque in its base, needs management of the giant papillae. If a plaque is present, this must be peeled away which requires a general anesthesia in the paediatric patient.

Keratoconus is a vision threatening complication that may require collagen cross linking, and the severe complication of limbal stem cell deficiency (LSCD) may require a conjunctival limbal allograft³⁰.

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