<table>
<thead>
<tr>
<th>Serial No</th>
<th>OKOSA, Chuka Chimdi M.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author 1</td>
<td>OKOSA, Chuka Chimdi M.</td>
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<td>Author 2</td>
<td>OKOSA, Chuka Chimdi M.</td>
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<td>Author 3</td>
<td>OKOSA, Chuka Chimdi M.</td>
</tr>
<tr>
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</tr>
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<td>Medical Sciences</td>
</tr>
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<tr>
<td>Signature</td>
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</tr>
</tbody>
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Vernal Keratoconjunctivitis (Spring Catarrh): A Review of Epidemiology, Pathogenesis and Management

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Vernal keratoconjunctivitis (VKC), a common oculoaural disease, is one of the allergic eye diseases. It has a worldwide distribution but is more common in hot countries. Fifty percent of sufferers are aged between 6 and 20 years. More males are affected than females before puberty and 98% of cases resolve within 10 years of the disease onset.

VKC is classified into 3 types: the palpebral or tarsal form, the follicular or follicular form and the mixed form. The corneal signs of the disease range from the benign punctate epithelial keratitis to the plaque formation.

Sight-threatening complications could result from corneal involvement or indiscriminate use of steroids.

Apart from steroid advised to be used only during exacerbations of the disease after safer treatment options include topical antihistamines and cyclosporin.

Key words: Vernal Keratoconjunctivitis; Allergic Eye Disease.

INTRODUCTION

Allergic eye diseases are very common and affect up to 20% of the population. The most common form is vernal keratoconjunctivitis (VKC), which is characterized by chronic conjunctival and corneal inflammation,蝶状lid margin, pre-lash, and a typical epithelial basement membrane change called "epithelialization." This condition is more common in children and young adults and is believed to be caused by an allergic reaction to environmental allergens.

DEFINITION

VKC is defined as a "persistent, bilateral, inflammatory reaction of the conjunctiva and cornea resulting from the accumulation of immune complexes and the activation of immune cells in the conjunctival and corneal tissue." The disease is characterized by the presence of mucous, vernal papillae, and a subepithelial accumulation of immune cells.

CLASSIFICATION

There are three clinical forms of the disease: (i) palpebral/limbal form, (ii) inferior palpebral form, and (iii) mixed form. The palpebral form is characterized by severe conjunctival hyperemia, papillae, and mucous discharge. The limbal form is distinguished by the presence of limbal vernal papillae, and the mixed form exhibits features of both.

This article provides information on the epidemiology, pathogenesis, and management of vernal keratoconjunctivitis.
B. Sandford-Smith in his case-series from Northern Nigeria could not make this distinction into only 3 clinical forms. This was because most of the patients with typical bullous disease also showed some mild papillary changes in the sub-basal conjunctiva on close examination and similarly most of the patients with typical papillary disease also showed some limbal changes. We, therefore, classified the patients into 5 groups as follows:

1. Bulbar disease only
2. Predominantly bullous disease
3. Mixed
4. Predominantly papillary disease
5. Papillary disease only
6. Vernal conjunctivitis could be classified based on severity into:
7. Mild VKC
8. Moderate VKC
9. Severe VKC

Epidemiology:

Distribution of VKC: The disease has a worldwide distribution but has large regional variations in its prevalence. It is common in warm, dry climates such as those of Italy, Greece, Israel and parts of South Africa. It is also common in central and South America, the Mediterranean but rare in the U.S. and Northern Europe. It is common in India, the tropics, China, Central Africa.

Description of different forms of VKC: There are widespread regional differences in the incidence of the different forms of VKC. Lymphoid VKC has been more frequently reported in Mediterranean countries, excluding Egypt and accounts for 11.7% of cases. Papillary VKC is common in temperate regions and is responsible for 7.78% of cases. The limbal form has been reported to be more common in blacks and the papillary in whites. Contrary, Magshooshur 

in his study of the disease in 52 Nigerian black children found the papillary form to be twice as common as the initial Sex distribution of VKC: More males are affected than females. The ratio of boys to girls is 2:1. However, the proportion of females affected may increase after puberty. From two large Japanese series of VKC patients it was found that the disease was more frequent in males than females below the age of 15 years but less frequent above 16 years. 

Age distribution of VKC: It has been detected in patients of all ages from 1 month to 75 years. However, 50% of sufferers are between 6 & 25 years of age. Over 40 years the disease is rare, 50% of cases involve within 10 years of the disease onset. Familial distribution: Although the disease may be familial and many authors have reported affected relatives, no clear Mendelian pattern of inheritance has been identified. Seasonal incidence: In temperate countries with a cold winter it starts in May and June and recedes in the autumn, the winter months being usually free from symptoms. In hot countries, however, it tends to persist all the year round (as in Egypt), and in such places as the Mexican highlands a single attack may last for years.

Pathology:

Histopathologic changes comprise essentially of:

a. Prominent cellullar infiltration of the substantia propria
b. Hypertrophy of connective tissue which becomes hyalinized and

c. Proliferative or degenerative changes of the epithelium.

Cellular infiltration: In the early stages of the disease the cellular infiltration is limited to the conjunctival epithelium and has a tendency to be perineural. As the disease progresses the inflammatory cells spread through to the substantia propria. In the chronic stage the subepithelial layers show bundles of hyalinized connective tissue, with inflammatory cells in the deeper strata. The histological picture is dominated by lymphocytes, plasma cells and eosinophils, but other inflammatory cells such as neutrophils abound cells, histiocytes and fibroblasts may also be seen. Hypertrophy of connective tissue: This is a salient feature of the condition. The collagen fibres proliferate and form an irregular network in the deeper layers of the conjunctiva. The spaces contain inflammatory cells, epithelial downgrowth, cysts and blood vessels. Papillary hypertrophy dominates in the deeper layers. The picture of individual papillae may become large forming giant papillae which are the hallmark of the papillary form of VKC.

Reticular fibres and proliferation of capillaries are found at all stages of the disease. Endothelial
swelling may be seen and the walls of blood vessels are sometimes lysed.

Proliferative or degenerative changes of the epithelium:
Epithelial changes tend to occur early. Proliferation as well as degeneration of the epithelium occur simultaneously.

In some instances the thickening may be so marked that it may be difficult to exclude neoplastic change especially when inflammatory cells are scanty. Columnar or triangular epithelial downgrowths may appear early in the disease. They do not penetrate the surface but may undergo degeneration. The goblet cells increase in number, especially in the conjunctival fornices between the papillae. As a result of the consequent degeneration and proliferation of the epithelium the stratified columnar cells become transformed into stratified squamous cells, and there may be keratinization.

PATHOGENESIS
A Type I hypersensitivity reaction underlies this condition but it also shows evidence of a non-specific basaloidal hypersensitivity (a non-classical type of cell-mediated immune response). There is no satisfactory explanation for the very different courses run by this disease, in particular, its development in children and its spontaneous remission in 95% of sufferers after 10 years.

Type I hypersensitivity reaction:
Most cells pairing receptors on their cell membranes for the F, portion of the IgE molecules. An allergen (allergic) reaching the conjunctiva of a sensitized individual reacts with mast cell bound IgE, stimulating the mast cell.
Phospholipase A, causes hydrolysis of membrane phospholipids with subsequent liberation of arachidonic acid and PAF. Arachidonic acids from metabolised via two pathways:
(1) the cyclo-oxygenase pathway resulting in the production of prostaglandins such as PGE2, and
(2) the lipoygenase pathway leading to the generation of leukotrienes such as LTC4 and LTD4. These leukotriene B4 products are potent inflammatory mediators.

In addition to the mast cell lysed - derived mediators mast cells contain granules that store inflammatory mediators such as histamine, proteoglycans and peptides. On stimulation the mast cell undergoes degeneration resulting in the release of these active mediators with subsequent initiation of inflammatory reaction (causing the typical symptoms of itching, hyperemia, swelling, tearing and mucous discharge). The acute inflammatory response may also induce the influx of neutrophils and eosinophils into the conjunctiva.

T-cell mediated hypersensitivity in VKC:
The normal human conjunctival epithelium is populated by CD4+ and CD8+ T-cells, mainly in the subepithelium. In the chronic allergic disorder VKC, CD4+ T-cells but not CD8+ T-cell numbers are increased, with a mixed cell infiltrate containing many mast cells, eosinophils, neutrophils and macrophages.

In the normal conjunctiva most of the T cells are naive, but in the chronic allergic disorders like VKC when there is an increase in CD4+ cell population, 95% of the T cells are memory T cells.

Also, studies have shown that in VKC there is an increased number of only TH-1 (TH-1 cells are the second distinct subset of CD4+ T-cells which produce a range of cytokines encoded on production, activation and survival. The first CD4+ T cell subset designated TH-1 cells produce: IL-2, IL-3, TNFα and interferon y IFN-γ and we more closely associated with the cell-mediated reaction (classic delayed-type hypersensitivity).

Role of Allergen molecules in the pathogenesis of VKC:
Allergen molecules expressed on blood vessel endothelial cells and leukocytes arrest the passage of circulating leukocytes in arterioles of inflammation. This is achieved by adhesion molecule ligand interactions that cause leukocytes to adhere to the vascular cell wall, followed by their transendothelial migration to the site of active inflammation.

In the normal conjunctiva there is a basal expression of all adhesion molecules while in allergic eye disease these levels are increased. VCAM-1 (Intercellular adhesion molecule-1) and E-selectin are expressed in 90% of vessels in VKC. VCAM-1 (vascular cell adhesion molecule-1) levels are highly elevated in VKC.

This results in a positive correlation E-selectin levels and the degree of lymphocyte infiltrate, whereas eotaxins with eosinophil levels.
specific influence of IL-4, is most selectively and strongly expressed in VKC. In VKC there are high numbers of CMI cells and eosinophils present.

**CLINICAL FEATURES**

- **Severe itch**
- **Lacrimation**
- **Redness**
- **Excoriation**
- **Severe keratoconjunctivitis**
- **Increased corneal thickness**
- **Excessive lacrimation**

**Signs**

- **Conjunctival signs**
- **Erythema**
- **Photophobia**
- **Conjunctival hyperemia**
- **Conjunctival edema**
- **Scleral injection**

**Giant papillae** with thick epithelium may occur on frontal conjunctiva in palpable form. In limbal form, pseudomembrane is noted. Follicles and hyperemia.

**Trantas dots** and **limbal cysts** may be seen in both forms of VKC.

**Clinical signs**

- **Plotting**
- **Van der Meer test**
- **Tear flow**

**Atopic patients** with a strong family history of **hay fever**, **asthma**, and **eczema**.

**Non-atopic patients**

- **Symptoms**
- **Eye pain**
- **Photophobia**

**Symptoms of VKC** are often worse in the morning and improve with **tearing**, **blurring**, and **itching**.

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<thead>
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<th>Disease</th>
<th>Features</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic Conjunctivitis (MCC)</td>
<td>- Hives</td>
<td>- Non-allergic conjunctivitis (NAC)</td>
</tr>
<tr>
<td>Allergic Keratoconjunctivitis (AKC)</td>
<td>- Itching</td>
<td>- Vernal keratoconjunctivitis (VKC)</td>
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<tr>
<td>Allergic Pterygium Conjunctivitis (APC)</td>
<td>- Redness</td>
<td>- Atopic keratoconjunctivitis (AKC)</td>
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</table>

### Features of the separate types of allergic eye disease (AED)

<table>
<thead>
<tr>
<th>Feature</th>
<th>MCC</th>
<th>AKC</th>
<th>AP/WHO</th>
<th>VKC</th>
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</thead>
<tbody>
<tr>
<td>Nitrates</td>
<td>- 25% of all AED</td>
<td>- 10% of AED</td>
<td>- 5% of AED</td>
<td>- 5% of VKC</td>
</tr>
<tr>
<td>Asthma</td>
<td>- Present</td>
<td>- Present</td>
<td>- Present</td>
<td>- Absent</td>
</tr>
<tr>
<td>Reaction</td>
<td>- Moderate</td>
<td>- Moderate</td>
<td>- Moderate</td>
<td>- Severe</td>
</tr>
<tr>
<td>Nitrates</td>
<td>- Present</td>
<td>- Present</td>
<td>- Present</td>
<td>- Absent</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>- Probable</td>
<td>- Probable</td>
<td>- Probable</td>
<td>- Probable</td>
</tr>
</tbody>
</table>

### DIAGNOSTIC TESTS

- Cytology shows eosinophils
- Scleral and tear IgE levels elevated
- Skin prick tests positive to wide variety of allergens

### MEDICAL TREATMENT

1. Mast cell stabilizers:
   - Sodium Cromoglicate
2. Antihistamines:
   - Iodocromide
3. Steroids:
   - Indications: anaphylaxis, atopic keratoconjunctivitis

Apart from the different types of allergic eye disease which could simulate VKC, pruritus involving the eyelids in undiagnosed cases is also a differential diagnosis.

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*J. All. Med. Assoc. 2000 3:1*
Patients need to receive treatment before the expected exposure. Dexamethasone is quick-acting and more effective than sodium metaprotinem (Hemorheal sodium), a new generation. Must gel stabilizers also come in a tube. Various agents when injected into the mass cell disallow relapse as well as eosinophil and mast cell generation.

(a) **Topical steroids:**
- Dexamethasone 0.1%
- Flunisolide 0.1%
- Pochlorsone 1%

These are effective in reducing the influx of inflammatory cells but have little effect on the mass cell reactivity. They are used to act and take several days to achieve their maximal effect. They may also have adverse effects such as producing skin growth, causing cracks and potentially infection and so are not used entirely.

(b) **Antihistamines:**
- **Typical antihistamines without anticholinergic:**
  - Levocabastine
  - Azelastine
  - Ketotifen
  - Terfenadine

(c) **Labetalol**

Cross-linkage of mast cell H1 receptors by antigen initiates a rapid sequence of events which terminates in mast cell degranulation. The later results in the release of proinflammatory mediators such as histamine and leukotrienes, and in the generation of mediators such as cytokines and platelet-activating factor from membrane lipid and platelet. Histamine effects are very important in allergic diseases and most of them are mediated through the H1 receptor. These effects include plasma, prostatographic generation and increased vascular permeability. Antihistamines occupy the same tissue receptors as histamine without providing any stimuli.

In the treatment of VKC, antihistamines could be administered topically or orally. Topical antihistamines could additionally be prepared with vasoconstrictors which act to reduce ocular blood.

The antihistamines listed above are second-generation H1-antagonists. The first-generation H1-antagonists that could be used include chlorpheniramine which has come both as tablets and syrup.

- **Topical vasoconstrictors**
  - Topical atropine,
  - Topical lidocaine,
  - Subcutaneous lidocaine,

- **Topical beta-blockers**
- **Topical corticosteroids**
- **Topical antihistamines**
- **Topical anticholinergics**
- **Topical vasoconstrictors**
- **Topical NSAIDs**
- **Topical mast cell stabilizers**

- **Topical steroids**
- **Topical antihistamines**
- **Topical vasoconstrictors**
- **Topical anticholinergics**

- **Topical NSAIDs**
- **Topical mast cell stabilizers**
- **Topical antihistamines**
- **Topical vasoconstrictors**
- **Topical anticholinergics**
- **Topical NSAIDs**
- **Topical mast cell stabilizers**

**Surgical:**
- Displacement of complicating corneal ulcers especially located in the visual axis.

**Suggested Treatment options:**

(Mild Cases)
- **Topical antihistamines**
- **Low-dose corticosteroids**
- **Lidocaine**
- **Topical mast cell stabilizers**
- **Topical antihistamines**
- **Topical vasoconstrictors**
- **Topical antihistamines**
- **Topical mast cell stabilizers**
- **Topical antihistamines**
- **Topical vasoconstrictors**
- **Topical antihistamines**
- **Topical mast cell stabilizers**

(Severe Cases)
- **Topical corticosteroids**
- **Topical mast cell stabilizers**
- **Topical antihistamines**
- **Topical vasoconstrictors**
- **Topical antihistamines**
- **Topical mast cell stabilizers**
- **Topical antihistamines**
- **Topical vasoconstrictors**
- **Topical antihistamines**
- **Topical mast cell stabilizers**

**Others:**
- **Home air-conditioning**
- **A change in geographical location and climate**

**Novel Concepts:**
- **Without Corneal involvement**
- **Topical steroids**
Topical triad CD4 T-cell agent e.g. cyclosporin 24

Topical lubricants.

(9) With caution Maximum especially if ulcer is located centrally.

Debridement of the ulcer

Topical antiseptics + steroids.

Moderately Therapeutic ETC.

Change in geographic location and climate may cause remission of disease.

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