

**EVALUATION OF HEALTH-RELATED QUALITY  
OF LIFE IN CHILDREN WITH VERNAL  
KERATOCONJUNCTIVITIS USING QUALITY OF  
LIFE IN CHILDREN WITH VERNAL  
KERATOCONJUNCTIVITIS QUESTIONNAIRE**

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**Dissertation Submitted In Partial Fulfilment Of  
The Requirement For The Degree Of  
Master Of Medicine  
(Ophthalmology)**



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## **DISCLAIMER**

I hereby certify that the work in this dissertation is my own except for the quotations and summaries, which have been dully acknowledged. I declare that I have no financial of interest in the instruments and the computer software used in this study.

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## **ABSTRAK**

### **PENGENALAN**

Keratoconjunctivitis vernal (VKC) adalah penyakit alergik mata kronik dan berlaku berulang kali yang kerap dihidapi oleh kanak-kanak lelaki sebelum mencapai umur akil baligh. Tanda dan gejala penyakit VKC ini akan memberikan kesan negatif terhadap kesejahteraan, gaya hidup dan mempunyai batasan aktiviti psikososial di kalangan pesakit kanak-kanak ini. Berdasarkan pemerhatian dan hasil carian di jaringan internet menunjukkan terdapat kekurangan data mengenai kualiti hidup yang berkaitan dengan kesihatan di kalangan pesakit kanak-kanak yang menghidapi penyakit VKC di Asia Tenggara .

### **OBJEKTIF**

Untuk menilai hasil purata markah secara keseluruhan dan subskala soal-selidik QUICK (Quality of Life in Children with Vernal Keratoconjunctivitis) dikalangan kanak-kanak penghidap VKC berbanding dengan kanak-kanak normal dan dikalangan kumpulan kanak-kanak dengan VKC.

### **KAEDAH KAJIAN**

Kajian ini merupakan kajian keratan rentas perbandingan yang dilaksanakan di Hospital Selayang dan Universiti Sains Malaysia antara Februari 2019 hingga Mei 2020. Kajian ini melibatkan kanak-kanak berumur 8-15 tahun. Pengambilan peserta VKC bergantung

kepada diagnosis VKC, yang dibuat berdasarkan riwayat klinikal pesakit, diagnosis sebelumnya, dan pemeriksaan secara objektif. Bagi peserta di dalam kumpulan kawalan, para peserta direkrut dari kanak-kanak sihat yang tidak mempunyai masalah mata yang tidak boleh dirawat atau sembuh.

## **KEPUTUSAN**

Seramai 240 kanak-kanak telah direkrut, termasuk 120 kanak-kanak dengan VKC dan 120 kanak-kanak normal yang sihat sebagai kumpulan kawalan. Terdapat perbezaan yang signifikan secara statistik dalam semua aspek data klinikal di dalam perbandingan antara kanak-kanak dengan VKC dan kanak-kanak normal ( $p < 0.001$ ) dan di kalangan kanak-kanak dengan kumpulan VKC ( $p < 0.001$ ). Terdapat perbezaan statistik dalam jumlah skor purata dan semua subskala antara kanak-kanak dengan VKC dan kumpulan kawalan ( $p < 0.001$ ) dan antara kanak-kanak dengan VKC ringan, sederhana dan teruk ( $p < 0.05$ ).

## **KESIMPULAN**

Soal selidik QUICK adalah alat soal selidik yang terbaik untuk menilai keadaan kualiti hidup berkenaan dengan kesihatan di kalangan kanak-kanak yang menghidap VKC. VKC memberi kesan negatif kepada kualiti hidup pada kanak-kanak yang menghidap VKC berbanding dengan kanak-kanak normal. Ini juga termasuk di kalangan kanak-kanak dalam kumpulan VKC yang mempunyai tahap yang lebih teruk. Memahami batasan psikososial, tanda dan gejala VKC yang mempengaruhi kebanyakan kualiti hidup ini ianya membawa pegawai perubatan yang merawat ke pendekatan secara holistik untuk menguruskan pesakit VKC.

## **ABSTRACT**

## **INTRODUCTION**

Vernal keratoconjunctivitis (VKC) is a recurrence, and chronic bilateral ocular allergic conjunctivitis mainly affected male prepuberty children. The signs and symptoms of VKC given a negative impact on well-being, lifestyle and limitation on psychosocial activities. There has been a lack of data on health-related quality of life (HRQoL) in children with VKC from Southeast Asia.

## **OBJECTIVE**

To evaluate the mean total and subscales score of the QUICK questionnaire between the severity of VKC and in children with VKC and healthy groups.

## **METHODOLOGY**

This study is a comparative cross-sectional study conducted in Hospital Selayang, Universiti Sains Malaysia between February 2019 and May 2020 involving children aged 8-15 years. The VKC participant's recruitment depends on the diagnosis of VKC, which was made based on the patient's clinical history, previous diagnosis, and objective examination. While in the control group, the participants were recruited from children with no existing ocular problems.

## **RESULTS**

Two hundred forty children were recruited, including 120 children with VKC and 120 normal healthy children as control. There were statistically significant differences in all aspects of clinical data in the comparison between children with VKC and normal children ( $p < 0.001$ ) and within the children with VKC group ( $p < 0.001$ ). There was a statistical difference in mean total scores and all of the subscales between children with VKC and the control group ( $p < 0.001$ ) and between the children with mild, moderate and severe VKC ( $p < 0.05$ ).

## **CONCLUSION**

The QUICK questionnaire is a good tool to assess the HRQoL among children with VKC. VKC disease negatively impacts HRQoL in children with VKC compared to normal children and in comparison within the severity of the VKC group. Understanding the psychosocial limitation and sign and symptoms of VKC that affected most HRQoL leads the physician to a holistic approach to managing the VKC patient.

# **CHAPTER 1**

## **INTRODUCTION**

## **1.1 VERNAL KERATOCONJUNCTIVITIS**

Vernal keratoconjunctivitis (VKC) is a rare and unique disorder among a spectrum of allergic ocular disease. It presents as chronic inflammation, bilateral ocular involvement in a severe form of allergies conjunctivitis. VKC is an ocular surface inflammation characterised by upper tarsal giant conjunctival papillae and/or limbal gelatinous hypertrophy that emerges common among children and young adults who have an atopic background. It is frequently observed in tropical regions where males are more commonly affected, and both gender ratio equally affected once in young adults (Addis and Jeng, 2018).

VKC is typically seasonal, and year-round symptoms can be seen, leading to uncertain diagnoses being made. Even though rare in temperate regions, it is an important cause of hospital referral in many parts of Africa and Asia. The disease is most often self-limiting and often resolved after puberty; however, some patients may develop sight-threatening VKC disease complications.

Understanding the nature of the disease may assist in managing the severity of VKC and its possible complication. Although this ocular allergic disease has been described for a long time, the exact aetiology and pathogenesis remain unclear. Immunosuppressive therapy is the mainstay of treatment in acute presentation, but surgical intervention may be required to manage the disease and its complications (Smedt *et al.*, 2013).

## 1.2 PATHOGENESIS

Aetiology involves a wide range of factors, including environmental allergens, climate and genetic predisposition. Most literature demonstrated that the pathogenesis of VKC is much more complicated than mere an allergic IgE disease, type 1 hypersensitivity reaction (Leonardi *et al.*, 2012). A prick test and/or measurement of specific IgE in serum should be used to investigate IgE sensitisation even though about 50 per cent of patients may be negative. The recent study on microarray technique in tear samples is a useful, simple and non-invasive diagnostic tool for specific IgE measurements with single protein allergens. These results reinforce the concept of possible local sensitisation (Leonardi *et al.*, 2015).

Cytological, bio-humoral, immunohistological and molecular biologic studies have shown that VKC is a Th2 lymphocyte-mediated disease. Mast cells and eosinophils and their mediators play a key role in clinical manifestations (Leonardi, 2013a). According to Nebbioso *et al.* other than allergic causes, the subsequent cytological and molecular biological study showed predominant Th2 expression and demonstrated the persistence of inflammation. The correlation of inflammatory reactions is evident by raising the percentage of ANA positivity by approximately 30.8% relative to children's general population (Nebbioso *et al.*, 2015). This research may provide a better understanding of VKC patients' relationship to a family history of autoimmune disorder linked to ocular inflammation, autoimmune disease, and atopic disorder.

Zicari *et al.* reported a study on serum level of Interleukin-17 (IL-17) in VKC patients. The IL-17 played an important role as a specific cytokine in many autoimmune



inflammatory diseases. IL-17, mainly produced by Th-17 cells, is a pro-inflammatory cytokine and has a potent effect on stromal cells, resulting in the production of inflammatory cytokines and the recruitment of leukocytes, in particular neutrophils. The study was done to evaluate the serum level of IL-17 in VKC patients compared with healthy control showed that the IL-17 more significantly elevated in VKC patients (Zicari *et al.*, 2013a). These findings supported the other study reported by Oh *et al.* on the association between dry eye syndrome and serum level of IL-17 in patients with systemic immune-mediated disease, and they found a correlation between serum level of IL-17 and disease severity (Oh *et al.*, 2011).

### **1.3 GEOGRAPHICAL DISTRIBUTION**

VKC has a wide geographical distribution with the prevalence of a variety of different ethnic group has been reported. It is more common in a dry, hot climate and warmth temperate zone such as Mediterranean areas, central and west Africa, the Middle East, Asian, the Indian subcontinent and South America (Alemayehu *et al.*, 2019, Baig *et al.*, 2010; Kassahun and Bejiga, 2012; Hayilu *et al.*, 2016). VKC cases are also seen in Western Europe, such as Finland, France, Italy, Netherlands, Norway, and Sweden, whose VKC prevalence estimates ranged from 1.16 to 10.55 cases per 10 000 populations in Europe (Bremond-Gignac *et al.*, 2008). In Asia, most specifically in South East Asia, there has been a very limited study of prevalence among Asian countries. The only available epidemiology data was from Japan, Thailand and Singapore for the time being (Miyazaki *et al.*, 2020; Kosrirukvongs *et al.*, 2001; Choi *et al.*, 2008).

## **1.4 DEMOGRAPHIC DATA**

VKC typically begins in the first decade of life and subside spontaneously after puberty. Even though most reported the VKC will resolve at puberty; excitingly, Saboo *et al.* reported that 12% of patients were above 20 years of age, about 3.5% of patients had an adult-onset disease (Saboo *et al.*, 2013). Similar cases reported by Leonardi *et al.* on the young adult onset of VKC with an equal sign and symptoms to those in paediatric onset, except with less cornea involvement (Leonardi *et al.*, 2013b).

In gender predilection, VKC is more common in males, with the male to female ratio varying from 4 :1 to 2 :1 in the literature (Shetty and Chandana, 2019; Venkataramana and Shruthi, 2020). This male-female ratio becomes almost equal after 20 years of age (Kansakar, 2011; Bonini *et al.*, 2000). A study on the possible role of sex hormone in VKC by assessing the serum level of sex hormone of VKC children and adolescents in 2015. The study showed that VKC patients demonstrated different circulating sex hormone levels in a different phase of disease compared to age-matched and sex-matched of the healthy group. These results indicate that sex hormones play a role in the pathogenesis and/or activity of VKC (Sacchetti *et al.*, 2015).

## **1.5 CLINICAL FEATURES, DIAGNOSIS AND ASSOCIATED CONDITION**

Typically VKC patients present with hyperemia, intense itchiness, watering, sticky mucoid discharge and photophobia, with 98% of cases are bilateral. They may experience several episodes of active inflammation throughout the year, some without any remission from the onset (Palmares *et al.*, 2010). Ocular itchiness may be exacerbated by exposure

to wind, dust, bright light or physical exertion with sweating (Prachee *et al.*, 2017; Sithole, 2020). Intriguing, Al-Hakimi *et al.* reported that *Staphylococcus aureus* could be exacerbating factors for active VKC and this study complement the other study by Shoji *et al.* and Tabuchi *et al.*. The study concluded that there could be a protective role of *S. epidermidis* against the growth of *S. aureus* and potentially, the occurrence of VKC (Al-Hakami *et al.*, 2015).

Although all the literature showed the clinical presentation of VKC and its complication are well defined, some overlapping criteria in grading and classification of the VKC were notable. Mostly VKC can be classified into a conjunctival, limbal or mixed form based on the predominant site of involvement with the findings of papillary hyperplasia is mandatory in the diagnosis (Zicari *et al.*, 2019).

There are currently no standardised guidelines for VKC diagnosis, and there is no uniformity in determining the severity of the disease, making it difficult to diagnose and treat the disease. The particular reason for this circumstance, Gokhale refined the grading of VKC, which is simple to use and based on clinical signs. The bulbar and tarsal conjunctiva and the cornea and limbus involvement are evaluated, and the severity is graded clinically (Gokhale, 2014) (Table I).

More recently, a new scoring system was introduced by Leonardi *et al.* to assess limbal and tarsal epithelial damage in patients with VKC. In patients with limbal involvement, the latest VKC-CLEK provides a more detailed assessment. The cornea and the limbal region are split into five areas in this new scheme. The overall score is provided by the sum of the staining scores allocated for each area, taking into account a score of 0–4 for

the central area and 0–1 for each limbal area. The total staining score is considered mild if less than three, moderate if equal to more than three and less than six and severe if more than six (Leonardi *et al.*, 2018). The papillae hyperplasia on the upper tarsal conjunctival and corneoscleral junction inflammation are hallmarks of VKC. Diagnosis is based on typical clinical signs and symptoms. Thus some in mild or atypical cases will be missed or late-diagnosed.

Table I: Grading allergic inflammation by Gokhale, 2014.

	Mild	Moderate	Severe	
Bulbar conjunctiva	Congestion	Congestion	Thickening Horner-Trantas Dots	Granulomas
Tarsal conjunctiva	Micro papillae	Macro (<1mm) papillae	Giant > 1mm papillae	Mega cobblestones
Cornea	-	Microerosions	Macroerosions	Shield ulcer
Limbus	-	Focal (<180°) inflammation	Diffuse (>180°) inflammation	Limbal deficiency

Since VKC is a part of the ocular allergic, the other allergic co-morbidity condition may be associated with the disease. A family history of atopic disease is seen in the majority, about 74% of patient with keratoconjunctivitis (Bremond-Gignac *et al.*, 2016). Among patients with VKC, 15–64% have asthma, 30–49% cases of allergic rhinitis, and 16–24% associated with eczema (Bonini *et al.*, 2000). These results supported by a study from Asian, with 9% out of 192 children were diagnosed with allergic rhinitis, among whom two-third had seasonal symptoms (Katelaris *et al.*, 2011). Besides atopy association, a family history of immunological disorders was found in 46% of patient, 28% of Hashimoto's thyroiditis, 14% of type I diabetes, 14% of psoriasis and one of systemic lupus erythematosus in children with VKC (Zicari *et al.*, 2013b).

## 1.6 TREATMENT OF VKC

Management of VKC cases includes preventive measure and patient education on current ocular problems. The very important aspect of management is an education to patient and parents on compliance of follow up, medical treatment and avoidance of exacerbation cause to prevent the possible ocular complication with poor visual prognosis. Pharmacological therapy available to treat the VKC includes antihistamines, mast-cell stabiliser, dual-acting agents (with antihistamine and mast cell stabiliser), non-steroidal anti-inflammatory agents, vasoconstrictor, corticosteroids and immunomodulator. Most of the therapy does not eliminate the complex immune response involving the disease's activity, thus in a patient with non-compliance to medical treatment, and once the drugs discontinued, the inflammatory ocular disease will recurrence.

The action of antihistamine is towards the histamine receptor antagonism to block the inflammatory effects of endogenous histamine and prevent the associated sign and symptoms. The most common antihistamine use in the treatment of allergy is an H1 receptor antagonist. Oral antihistamine is a good choice when allergy involves the eyes, nose or pharynx simultaneously. Topical antihistamine provides faster and superior relief than systemic in ocular allergy by inhibiting proinflammatory cytokine secretion from conjunctival epithelial cells. Even though it is safe and well-tolerated, some reported the burning and stinging sensation, blurred vision and unacceptable aftertaste. Long term efficacy and safety is still lacking in reporting data, single-dose preservative-free eye drops recommended to use to minimise possible ocular toxic effect (Leonardi *et al.*, 2019a).

Mast cell stabiliser prevents mast cells' degranulation, releases preformed inflammatory mediators and synthesised additional inflammatory mediators. Initially known as the first-line treatment of VKC at onset and continuously applied throughout the season. It is safe and has a minimal ocular side effect, the compliance issue and tolerability concern may be facing since burning sensation upon application of the medication. Many studies have shown the drug's effectiveness to control the symptoms and prevention exacerbation. The example of mast cell stabilisers such as chromones requires multiple daily doses and delayed onset of action, hence less preferable (Bielory *et al.*, 2020).

Topical corticosteroids are one of the most effective drugs to control the ocular inflammation of VKC and effectively relieve the sign and symptoms of all phase of VKC within six hours. Because of associated complication such as steroid-induced cataract, glaucoma, and increase susceptibility to infection on prolonged use, the application of corticosteroids should be used with a better precaution. The development of increased IOP and glaucomatous changes in corticosteroid usage may differ depending on whether the patient is a steroid reactant linked to the glaucoma family history. Supra-tarsal injection dexamethasone sodium phosphate, triamcinolone acetonide, or hydrocortisone sodium succinate was used with precaution in refractory VKC is effective in the temporary suppression of inflammation (Leonardi *et al.*, 2019a).

The recent immunomodulator drugs of choice in the treatment of VKC is cyclosporine. Topical cyclosporines are very encouraging. However, due to the unavailability commercially in high concentration preparation, its use is limited. It effectively alleviates the signs and symptoms of VKC while maintaining a similar safety profile, reducing reliance on topical steroid eye drops (Wan *et al.*, 2013; Leonardi *et al.*, 2019b).

For the management of severe, refractory cases of AKC and VKC, Tacrolimus 0.03 per cent - 0.1 per cent eye drops or ointments have been suggested. A commercial eye drop preparation with an indication of severe AKC and VKC is available only in Asia. In two randomised control triad and four case series, one study, with a critically low quality of evidence score, highlighted tacrolimus's benefits over placebo (Zhai *et al.*, 2011).

The surgical procedure is another option in managing the more severe cases of VKC. Surgical removal of corneal plaques or ulcer base debridement with amniotic membrane transplant is recommended to alleviate severe symptoms and allow corneal re-epithelisation. The corneal complication treatment algorithm can be based on the Cameron clinical classification of Grade 1 shield ulcers received medical therapy alone; Grade 2 and Grade 3 ulcers received medical therapy alone or medical therapy combined with debridement, AMT, or both (Reddy *et al.*, 2013). Significant limbal stem cell deficiency as a complication of severe and persistent limbal inflammation in VKC disease has been treated with stem cell transplantation (Sangwan *et al.*, 2011).

## **1.7 HEALTH-RELATED QUALITY OF LIFE**

WHO defines the quality of life (QoL) as individuals' perception of their position in life in the context of the culture and value systems they live in and concerning their goals, expectations, standards, and concerns (Organization, 1997). The terms of health-related quality of life (HRQoL) is commonly referred to as the context of health and disease. HRQoL is multidimensional and includes a field related to physical, mental, emotional, social functioning and the social context in which people live (Healthy People, 2020).

Understanding the nature of VKC disease, commonly affected in first decade prepuberty age more in males with recurrent chronic inflammation, may impair life quality. As the onset is well known in the school-age groups, it negatively impacts schooling, with some authors reporting the patient absentee from school and impaired school performance. A study on school impact in VKC children reported by Marey *et al.* among school children in Egypt revealed the school absentee was less than one week were found in 44.7% of cases, and more than one week was found in 18.4% of cases (Marey *et al.*, 2016).

HRQoL questionnaires are relevant for a clinician to aid in the evaluation of VKC severity and treatment outcomes. HRQoL parameters have become important outcome measures in allergic diseases, and many questionnaires have been developed to evaluate the impact of allergy on HRQoL. However, there is a clear lack of literature regarding the QOL questionnaire over ocular allergy, with most questionnaires focused on rhinoconjunctivitis. A few validated questionnaires available in assessing the VKC patient includes a QUICK questionnaire and Eye Allergy Patient Impact Questionnaire (EAPIQ) (Sacchetti *et al.*, 2007; Mikhail *et al.*, 2020).

## **1.8 RATIONALE OF THE STUDY**

Over the last 25 years, health-related quality of life has become more recognition, as it aids health practitioners to understand how the health condition may impact a patient. Specifically, ocular allergy has been found to affect an individual emotionally, physically, socially, and economically.



A limited study has been conducted in South East Asia, especially in Malaysia, on the evaluation of HRQOL in children with VKC. Thus, this analysis was carried out to provide accurate local data criteria to determine and provide better VKC treatment and management. The demographic and clinical data from this study of a patient with VKC can be viewed as a guide to global knowledge on allergic diseases in Asia.

VKC distress the HRQoL of affected individuals in multiple ways. Understanding the nature of the disease and its impact on daily living among children with VKC is important in improving QoL and rehabilitation. These help the clinicians to understand patient perceptions and experience. The HRQoL might differ in a similar severity group due to differences in culture, social belief and personal experience.

The children with VKC may present bilateral eye redness during the active form, giving a bad stigma of contagious infected eyes among the surrounding, social events, or school. Thus this study can also provide important inputs or information regarding the non-contagious red eyes disease among school children and organisation. Hence the patients may eliminate the negative perception and increase self-confidence, thus improving and promote a healthy lifestyle.

The other reason for evaluating HRQoL in children with VKC is that it helps recognise a child's needs and expectations. The attending physician may consider how a treatment decision may impact the children and family QoL. These assessments may also be used to determine particular modalities and strategies in managing the individual VKC patient.

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# **CHAPTER 2**

## **OBJECTIVES OF THE STUDY**

## **2.0 STUDY OBJECTIVES**

### **2.1 GENERAL OBJECTIVE**

To evaluate the health-related quality of life in children with VKC using the QUICK questionnaire.

### **2.2 SPECIFIC OBJECTIVES**

- 2.2.1 To compare the mean total and subscale index score of the QUICK questionnaire between children with VKC and the control group.
- 2.2.2 To compare the mean total and subscale index score of the QUICK questionnaire in different severity level of VKC.

### **2.3 HYPOTHESIS**

- 2.3.1 The mean total and subscale domain score of the QUICK questionnaire in children with symptoms of VKC is significantly impaired than in the control group. The percentage of the QUICK questionnaire in children with VKC is significantly highest in a patient with eye itchiness symptoms compared with other symptoms.
- 2.3.2 The mean total and subscale domain score of the QUICK questionnaire in children with VKC is statistically significant in the severity group with the higher mean score indicates the poorer quality of life.

# **CHAPTER 3**

## **MANUSCRIPT**

# **Evaluation of Health-Related Quality of Life in Children with Vernal Keratoconjunctivitis Using Quality of Life in Children with Vernal Keratoconjunctivitis Questionnaire**

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### **3.2 Abstract**

There has been a lack of data on health-related quality of life (HRQoL) in children with vernal keratoconjunctivitis(VKC) from South East Asia and Malaysia in particular. This study evaluated the level (mean total score and subscales score) of HRQoL, comparing the VKC and normal children groups and within the VKC severity groups. A cross-sectional study was conducted in two tertiary hospitals (pediatric ophthalmology service) includes Hospital Selayang and Universiti Sains Malaysia, between 2019 and 2020. The participant aged 8-15 were divided into two groups; VKC and healthy normal children as the control group. A participant completed the QUICK questionnaire. There were 16 questions, divided by two subscales with 12 questions for the symptoms subscale and four questions for the daily activities subscale. A total of 240 children participated in the study, including 120 children with VKC and 120 control groups. The mean age of VKC participant was 11.21(1.91) years old with male predominance was 4:1 ratio to female. Tearing (98.4%) and itchiness (98.3%) are the most affected symptoms in HRQoL, while the most troublesome activities were playing outdoor (36.6%) and involving with recreational water activities (34.2%). The mean total score was significantly higher in the VKC compared to the control groups. The mean total score and all subscale score in the severe type were significantly higher than the mild-moderate type. The QUICK questionnaire is a good tool to assess the HRQoL. VKC significantly reduce the HRQoL among Malaysian children, and the negative impact increases with the disease severity.

#### **Keywords:**

Vernal keratoconjunctivitis; quality of life; health-related quality of life; ocular allergy