



The effect of COVID-19 imposed lockdown on Italian children with Vernal Keratoconjunctivitis

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ABSTRACT

Background: Vernal keratoconjunctivitis (VKC) is a chronic, inflammatory-allergic disease of the cornea and conjunctiva. Environmental factors, such as light exposure, have been supposed to play a role in the pathogenesis of ocular inflammation and in the worsening of VKC.

Objective: The aim of this study was to estimate the impact of reduced sunlight exposure in patients with VKC during the imposed lockdown period for the SARS-CoV-2 pandemic emergency.

Methods: We retrospectively reviewed data of patients with VKC visited during spring season in 2020 and 2019 at Vernal Keratoconjunctivitis Multidisciplinary Outpatient of our Hospital. Subjective symptoms were evaluated by Visual analogue scale (VAS) and VKC severity was graded by Bonini scale. Quality of life was evaluated by Correlations of Quality of Life in Children with Vernal Keratoconjunctivitis (QUICK) questionnaire. The number of hours of e-learning as well as of hours spent in front of a bright screen (PC, TV, mobile, tablet play station, and so on) was also investigated.

Results: Twenty-nine male subjects (mean \pm SD age: 8.74 ± 2.40 years) with VKC were included in the study. Most of the patients (17/29) were sensitized individuals.

No significant changes in Bonini severity score and in VAS evaluation were observed comparing 2020 to 2019 values. Ten (34.4%) patients did benefit from the reduced sunlight exposure. The increased use of bright screens was associated with worsening of VKC severity.

Conclusions: Sunlight exposure plays a role in VKC exacerbation in about one third of patients. The number of hours spent in front of bright screens may influence severity of VKC symptoms.

Keywords: Allergy diagnosis, Quality-of-Life, Vernal keratoconjunctivitis, Conjunctivitis, Covid-19

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INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a rare disorder of the ocular surface mostly affecting boys in the prepubertal age. VKC is characterized by bilateral, chronic, recurrent inflammatory-allergic reaction of the cornea and conjunctiva.¹ Patients with VKC during recurrences of the disease complain of intense photophobia, redness, watering eyes, and itching.^{2,3}

Vernal keratoconjunctivitis is traditionally classified as limbal, tarsal, or mixed based on the location of conjunctival papillary reaction.² VKC is characterized by inflammatory infiltration of the conjunctiva, especially by eosinophils. Although VKC was previously considered as an IgE-mediated disease, the involvement of several other immunologic, hormonal, genetic and environmental pathways have been demonstrated. Specifically, increased levels of inflammatory cytokines (IL-3, IL-4, and IL-5) and activated CD4⁺ T-helper type 2 (Th2) lymphocytes have been described in patients with VKC.⁴ This evidence could suggest a possible hypersensitivity reaction to pathogens which are currently still unknown.^{5,6} Recent evidence also suggested a role of innate immunity as well as of sex hormones⁷ or of genetic predisposition.⁸ In addition, a potential role of environmental factors may be hypothesized.⁹ In fact, VKC development and exacerbations seems strongly related to sunlight exposure, responsible for the worsening of the disease and the presence of intense photophobia in the majority of patients.¹⁰ In addition, epidemiological studies showed that VKC prevalence is highest in sunny and hot places (ie, 5.8% reported in Northwest Ethiopia versus 11.1% in Southwest Ethiopia) and it is almost absent in countries with short sunlight exposure (close to 0% in Scandinavian country), supporting the hypothesis of a pathogenic role of sunlight exposure in the development of this condition.^{11,12}

Theoretically, in order to estimate the real impact of sunlight exposure in the pathogenesis of VKC, patients should not be exposed to sunlight. In real life, this would have remained an impossible scenario to reproduce or even to imagine, until the outbreak of the SARS-CoV-2 pandemic. During the first wave of the pandemic, the Italian Government imposed a lockdown to all its citizens from the beginning of March to the end of May 2020. In

particular, schools were closed from March 5 to the end of the 2019–2020 school year and electronic distance learning (e-learning) was adopted. During this same period, students extensively used electronic devices with bright screens (ie, mobiles, smartphones, computers, electronic entertainment devices, and similars), also taking into account digital devices for educational purposes (online classes, assignments, and so on).

The purpose of this study was to evaluate the “lockdown effect” on VKC, that is to verify if the subjects who were forcibly sheltered from sunlight showed VKC symptoms anyway; furthermore, we also analyzed the severity of symptoms in 2020 compared to the same period of the previous year, due to the shorter period of sunlight exposure in 2020 compared to 2019. In addition, we investigated whether the hours spent in front of the light produced by the bright screens influenced the extent of the symptoms, in condition of almost zero sunlight exposure.

METHODS

Patients

In the Vernal Keratoconjunctivitis Multidisciplinary Outpatient of our Hospital, clinical data, instrumental ophthalmological objectivity, and quality of life are systematically collected.¹⁰ We retrospectively reviewed the data of patients with VKC evaluated from May 2020 to July 2020, which had already been visited from March 2019 to July 2019. Children and adolescents aged between 5 and 12 years with previous diagnosis of VKC, based on clinical history and eye examination (presence of mild to severe giant papillary reaction at the upper tarsal conjunctiva and/or at limbus and/or presence of Horner-Trantas dots), were included. Specifically, all patients were diagnosed in 2019 before starting any specific therapy, except unsuccessful topical antihistamine treatment. In 2020, the same patients were evaluated before starting any specific therapy from May to July, due to the lockdown imposed by the Italian Government which stopped all outpatient activities in the months all over the period March–April 2020, with exception of emergency needs. Therefore, at the first visit in 2020, most of the patients had not yet started a specific therapy.

Only 4 patients were in continuous treatment with immunosuppressive eye drops due to the presence of chronic symptoms: three used topical cyclosporine A eye drops, one topical tacrolimus eye drops.

Bambino Gesù Children's Hospital Ethics Committee authorized us to review the clinical records of children matching our inclusion criteria.

Clinical evaluations

At time of visit, subjective symptoms were evaluated by administration of a predefined 0-to-10 Visual Analogue Scale (VAS) to score the presence of photophobia, tearing, ocular itching, and mucous ocular secretions. A VAS total score was calculated as the sum of VAS scores of all the 4 VKC symptoms values (from 0 to 40).

Clinical severity of VKC was graded according to Bonini grading scale.¹³ We considered the patients improved, worsened or stable in 2020 compared to the 2019 season if the Bonini grading scale decreases, increases or remains stable, respectively.

Six (24%) patients had more severe symptoms (ie, increase in Bonini grading scale):

Clinical history was collected including the presence of associated atopic conditions including atopic dermatitis, allergic rhinitis, asthma, and food allergy. Caregivers and children were asked for the availability of a garden in their family homes and for the number of hours per day spent in front of a bright screens, which usually entails combination of watching TV, playing video games, and/or using smartphone and PC - including hours of e-learning.

The same skilled allergist (MAC) performed skin Prick Tests (Lofarma, Milan, Italy) for a standard panel of inhalant allergens, including grasses, *parietaria*, mugwort, birch, olive, *plantago*, ragweed, hazel, cypress, dust mites, dog and cat dander, *alternaria*.

Instrumental ophthalmological evaluation

The same skilled ophthalmologist (ME) performed slit lamp examination of the anterior segment of the eye to evaluate the presence of conjunctival hyperemia, conjunctival tarsal and/or limbal papillary reaction (with or without giant papillary reaction), Trantas dots and corneal

superficial keratopathy. Signs were scored from 0 to 3 (0 absent, 1 mild, 2 moderate, 3 severe). The total signs score was calculated as the sum of all the sign scores (range between 0 and 12). The presence of epithelial defects and/or corneal ulcers was also evaluated.

Health Related Quality of Life evaluation

We evaluated Health Related Quality of Life (HRQoL) by administering the validated Italian version of the Correlations of Quality of Life in Children with Vernal Keratoconjunctivitis (QUICK) questionnaire containing 16 items divided in two domains: Quick Score 1 (Symptoms Factor: 12 items) and Quick Score 2 (Daily Activities Factor: 4 items). The total Quick score was then calculated according to authors' formula.¹⁴

Statistical analysis

Statistical analysis was performed using the statistical software R (R Core Team, version 4.0.3). Changes in the overall distribution according to clinical severity (Bonini grading scale) were analyzed by Fisher's exact test. Linear mixed effect regression models were devised using the *lme4* package to measure the effects of different parameters (hours of e-learning, difference in average time spent in front a computer screen between 2020 and 2019, and availability of a garden) on pain and HRQoL, with each subject being included as a random variable. Statistical significance was set at $p < 0.05$.

Statistical power analysis

Sample size was calculated using the G*Power software (version 3.1), using a 0.5 effect size (representing medium effect size, according to Cohen¹⁵) for linear multiple regression with three predictors, with $\alpha = 0.05$ and power 0.95. According to these calculations, a total sample size of 24 was needed. By including 29 subjects, the post-hoc analysis yielded a 0.98 statistical power.

RESULTS

Patients

Twenty-nine male subjects (mean \pm SD age: 8.74 ± 2.40 years) with VKC were included in the study. Most of the patients (17/29) were sensitized

individuals. None of our patients had been infected with SARS-CoV-2.

The form of VKC in 2019 was tarsal and mixed in 12 and 17 patients respectively; in 2020 it was tarsal in 19 and mixed in 10 patients. No patient presented with an exclusively VKC limbal form in both years.

Clinical severity according to the Bonini grading scale was as follows: 6.9 and 13.7% mild (grade 1), 51.7% and 48.2% moderate (grade 2), 41.3% and 34.4% severe (grade 3-4) in 2019 and 2020, respectively. One patient presented a quiescent VKC (grade 0) in 2020 (Table 1).

Changes of ocular symptoms' visual analog scale (VAS) during lockdown period

No statistically significant effects were found for any of the "surrogate" markers of light exposure (Symptom Δ across years, garden available, Δ screen time between years) regarding total VAS (Table 2a). The analysis of the different subscales of pain (photophobia, tearing, ocular itching, and mucous ocular secretions) yielded similar results, as shown in Table 2b.

Similarly, no statistically significant effects were found for changes in Quick score 1, Quick score 2 and Total Quick score between 2019 and 2020 in regard to the variables included in the study (Tables 3-5).

Overall, the severity of symptoms, as expressed by the Bonini grading scale, did not significantly differ between 2019 and 2020 ($p = 0.2725$).

Bonini score	2019 (n = 29)	2020 (n = 29)
0	0 (0%)	1 (3.45%)
1	2 (6.90%)	4 (13.79%)
2a	6 (20.69%)	9 (31.03%)
2b	9 (31.03%)	5 (17.24%)
3	10 (34.48%)	5 (17.24%)
4	2 (6.99%)	5 (17.24%)

Table 1. Distribution of subjects according to clinical severity (expressed by Bonini score) across years. Fisher's exact test, $p = 0.2725$

Parameter	β (std. error)	p-value
Symptom Δ across years	1088 (1978)	0,587
Garden available	0,872 (5512)	0,876
Δ screen time between years	0,34 (0,64)	0,600

Table 2a. Effects of surrogate markers of light exposure on total VAS scale in patients with VKC

Evaluation of "lockdown effect" on Vernal Keratoconjunctivitis (VKC)

In order to verify whether the subjects who were forcibly sheltered from sunlight had the symptoms anyway, we excluded from the analysis patients who have a house with a garden and which may have been exposed to sunlight anyway (4/29) and we analyzed each patient individually.

Overall, 10 patients (34.4%) benefited from the lack of exposure to sunlight because presented symptoms only upon re-exposure to it.

Fifteen patients presented symptoms also during lockdown period: 9 in the same time of 2019, 4 had chronic symptoms, and 2 had symptoms ahead of the 2019 season.

In 2020, 8 patients (32%) had milder symptoms (decreased Bonini grading scale) compared to 2019; of these, 5 had symptoms only when they were re-exposed to sunlight while 1 patient had symptoms in the same period of the previous year, and 2 patients had chronic symptoms. Eleven (44%) patients had symptoms of the same severity (ie, same Bonini grading scale) as the previous year: 5 only after re-exposure to sunlight, 3 in the same month of 2019, 2 had chronic symptoms, and 1 had symptoms ahead of the 2019 season (Table 6).

Six (24%) patients had more severe symptoms (ie, increase in Bonini grading scale): 5 of these had symptoms during the same period of 2019 and one started showing symptoms of VKC in 2020, 3 months earlier than in 2019 (Table 6).

Overall, patients spent a mean of 1.95 ± 1.79 h/day using PC or bright screens in 2019 and 4.14 ± 2.49 h/day in 2020 ($p = 0.048$), but we

Parameter	Photophobia		Ocular itching		Tearing		Mucous ocular secretions	
	β (std. error)	<i>p</i> -value	β (std. error)	<i>p</i> -value	β (std. error)	<i>p</i> -value	β (std. error)	<i>p</i> -value
Δ across years	-0,014 (0,69)	0,984	0255 (0,69)	0,715	0499 (0,623)	0,430	0134 (0,76)	0,861
Garden available	1,06 (1595)	0,512	0481 (1559)	0,761	0941 (1711)	0,587	-1774 (1756)	0,323
Daily hours of remote learning	-0,209 (0,498)	0,678	0236 (0,487)	0,633	0504 (0,532)	0,353	0312 (0,548)	0,575
Diff. in screen time between years	0,171 (0,185)	0,364	-0,001 (0,181)	0,995	0037 (0,199)	0,855	0239 (0,204)	0,253

Table 2b. Effects of surrogate markers of light exposure on VAS scale for all the four VKC symptoms values in patients with VKC

found no significant difference across the three severity groups ($p = 0.823$).

But analyzing each patient individually, in the subgroup of patients who presented symptoms only upon re-exposure to sunlight, those who reported an increase in hours in front of bright screens ≤ 4 times compared to 2019 (average increase 1.35 h/day) displayed a decrease in symptoms severity. For a 4+ times increase, patients experienced symptoms of the same entity of the previous year (average increase 5.75 h/day). Interestingly, in the patients with VKC recurrence also during lockdown period, the number of hours spent in front of light sources seem to be a determinant factor of worsening of symptoms. In fact, in 73.3% (11/15) an average increase of 4.09 h

is related to symptoms more severe or of the same severity of the previous year. Interestingly, the six patients (24%) who complain more severe symptoms (ie, increase in Bonini grading scale) in 2020 spent more hours in front of light screens than in 2019 and compared to patients who had milder symptoms in 2020.

Of the 14 patients who are also allergic to inhaled allergens, seven had symptoms only upon re-exposure to sunlight, four of whom with symptoms of lesser intensity and three with symptoms of the same intensity compared to spring 2019. The remaining seven allergic patients had symptoms also during the spring 2020: 5 with severity equal to that of the previous year and 2 of more severe intensity. These were the 2 patients allergic to dust

Parameter	β (std. error)	<i>p</i> -value
Δ across years	-2066 (4239)	0,630
Garden available	7448 (8123)	0,368
Δ screen time between years	1072 (0,943)	0,266

Table 3. Effects of surrogate markers of light exposure on Quick score 1 in patients with VKC

Parameter	β (std. error)	<i>p</i> -value
Δ across years	-5024 (3276)	0,136
Garden available	-7354 (12,202)	0,552
Δ screen time between years	0,819 (1417)	0,569

Table 4. Effects of surrogate markers of light exposure on Quick score 2 in patients with VKC

Parameter	β (std. error)	p-value
Δ across years	-3503 (3815)	0,366
Garden available	1023 (10,484)	0,923
Δ screen time between years	1989 (1217)	0,115

Table 5. Effects of surrogate markers of light exposure on total Quick score in patients with VKC

mite and cat dander and therefore to indoor allergens.

DISCUSSION

The lockdown period imposed by the Italian Government to tackle the SARS-CoV-2 pandemic represented a unique opportunity to evaluate the impact of sunlight exposure in the pathogenesis of VKC. In fact, children in Italy remained confined to their homes from March 5 to the end of May 2020 when free movement was permitted again. Italian children, forced to stay indoors, were then exposed to sunlight for a shorter period during Spring season (3 months - March, April, May - in 2019 versus 0 months in 2020). As a consequence, the children spent many hours in front of bright screens (television, smartphones, tablets, and computers screens), also due to the proposed e-learning initiatives.

Our results have not identified a global statistically significant difference between 2019 and 2020 in VAS and in QoL scores; however, we expected these results because we visited the patients in both years during the acute phase of the VKC.

By excluding from the analysis patients who have a house with a garden that were therefore exposed to sunlight anyway (4/29), 25 patients had almost sun exposure. In the absence of sun exposure, one of the main triggers of VKC, patients might be expected to have no symptoms or to be less severe when they appear, with a reduction of the Bonini score in spring 2020 as compared to the same period of the previous year. Our results indicate that more than one-third of patients (34.4%) benefited from the lack of exposure to sunlight because showed VKC symptoms only

upon re-exposure to it and in any case to the re-exposure no one had more severe symptoms than the previous year; indeed, one-half of the patients had milder symptoms and the other half symptoms of the same severity.

In this group of patients who benefited from lower sunlight exposure time, a reduced exposure also to different light sources during lockdown was associated with milder symptoms upon recurrence; on the contrary, patients who had a four-fold increase in exposure to bright light screens in 2020 reported symptoms of the same severity as the previous year, effectively eliminating the beneficial effect of the lack of exposure to sunlight.

In our caseload, sunlight seems not associated with VKC symptoms in about two-thirds of patients. In fact 15 patients presented symptoms during lockdown period anyway; in this group, 2020 symptoms severity was equal, milder or more severe than 2019 in 6, 3, 6 patients, respectively.

Also for most of these patients (73.3%) a four-fold increase in exposure to screens resulted in symptoms severity equal or greater than the previous year.

To the best of our knowledge, at the time of writing, this study is the first which aimed at evaluating the impact of sunlight and light bright screens on VKC. Several studies demonstrated an association between the overuse of other electronic devices such as mobile and myopia in children, even in preschool age,^{16,17,18} especially if outdoor time is reduced.¹⁹ Furthermore the literature in this field has been recently enriched with studies correlating vision impairment with the increased use of digital screens during COVID-19 outbreak.

In fact, 93.6% of people experienced an increase in their digital device usage per day during lockdown period. In particular, the student population have logged an average increase in usage of digital devices of 5.18 ± 2.89 h per day, bringing their daily usage to 8.9 ± 3.63 h. It has been also reported that 56.5% of subject, mostly students (60%), reported a statistically significant increase in number ($P = 0.001$), frequency ($P = 0.028$) and intensity of digital eye strain symptoms ($P = 0.005$) since the lockdown was declared.²⁰

Parameters	All patients (N = 25)		Improved group (N = 8)		Stable group (N = 11)		Impaired group (N = 6)	
	2019	2020	2019	2020	2019	2020	2019	2020
VKC type (N)								
Tarsal	11	14	0	7	7	6	4	1
Limbal mixed	0	0	0	0	0	0	0	0
	14	11	8	1	4	5	2	5
Bonini score (N)								
0	0	1	0	1	0	0	0	0
1	1	2	0	2	0	0	1	0
2a	6	9	0	4	4	5	2	0
2b	8	3	1	0	4	3	3	0
3	7	6	5	1	2	2	0	3
4	3	4	2	0	1	1	0	3
VAS total score (mean ± SD)	17.5 ± 10.09	20.1 ± 10.8	17.3 ± 7.4	19.6 ± 8.2	21.09 ± 10.1	16.2 ± 11.2	11.3 ± 9.8	27.8 ± 9.08
Allergen sensitization (N)								
DM	15		4		9		2	
Cat	3		0		1		2	
Grasses	2		0		2		0	
Olive	1		0		0		1	
None	10		4		2		4	
Exposure to bright screens (mean ± SD hours)	1.9 ± 1.8 ^a	5.4 ± 2.5 ^a	1.75 ± 1.16	3.62 ± 2.26	2.8 ± 3.33	3.7 ± 2.11	2.29 ± 0.95	3.14 ± 1.46

Table 6. Clinical characteristics of study population (including only patients without a house with a garden which may have been exposed to sunlight anyway). DM, dust mite. ^aP < 0.048 at t-test

These data are in line with ours; in fact, even our patients, very young students, reported a statistically significant four-fold increase in the hours spent using electronic equipment during the lockdown compared to the previous year. Interestingly, in our study this resulted in a worsening of ocular VKC symptoms (6/25) or at least symptoms of the same severity as in spring 2019 (11/25) even in those who, thanks to the reduced exposure to sunlight in spring 2020 compared to that of 2019 (0 months against 3 months), had managed to have no symptoms until re-exposure to sunlight (5/11).

To the best of our knowledge, at the time of writing, this study is among the first to examine the association between digital screen time and VKC symptoms in children and adolescents. Until now, only in vernal keratoconjunctivitis-like disease adult patients with more vision-related activities (computer, photography) was reported the worst productivity index during the active phase of the disease.²¹

Recent findings show how the ocular surface can serve as a reservoir and source of contagion for SARS-CoV-2^{22,23} and conjunctivitis may be a sign of COVID-19. In our caseload, no patient got SARS-CoV-2 infection. In particular, neither of the 4 patients have under immunosuppressive eye drops – in 3 cases cyclosporine and in 1 case tacrolimus – did not show more susceptibility to infections, including coronavirus. On the other hand, Leonardi et al suggested that the over-expression of multiple antiviral factors and the low ACE2 expression in the conjunctiva might explain the low prevalence of COVID-19 in VKC with tendency for VKC to be protective, reporting an odds ratio (OR) = 0.88 (95% CI, 0.66–1.16) for VKC to be associated with COVID-19 OR in the greater Padova area.²⁴

We can conclude that exposure to non-specific triggering factors such as sunlight and bright light screens is a favoring factor for conjunctival inflammation trigger in VKC. Our results suggest that use of sunglasses, hats with visors, and swimming goggles should be recommended,²⁵ as well as the reduction of time spent in front of bright light sources such as smartphones, computers, and television in children with VKC.

After all the actual guideline recommend for health benefits, children (5–11 years) and youth (12–17 years) should limit recreational screen time to no more than 2 h per day.²⁶ Unfortunately, already in 2015 these guidelines were not respected by at least the 54.2% of the children aged 9–11 years.²⁷

Abbreviations

VKC, Vernal keratoconjunctivitis; VAS, Visual Analogue Scale; DM, dust mite.

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Author contributions/custom author support

Maria Cristina Artesani: Conceptualization (lead); Data curation (lead); Investigation (equal); Writing-original draft (equal).

Mariacristina Esposito: Investigation (equal); Supervision (equal).

Marta Sacchetti: Supervision (lead); Writing-original draft (supporting).

Andrea Sansone: Data curation (lead); Formal analysis (lead); Methodology (equal). Antonino Romanzo: Supervision (supporting).

Luca Buzzonetti: Supervision (supporting).

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Ethics approval and consent to participate

Bambino Gesù Children's Hospital Ethics Committee authorized us to review the clinical records of children matching our inclusion criteria.

Consent for publication

Authors consent to publication.

Declaration of competing interest

Authors disclose any competing interests related to the manuscript content.

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