



Eyelid Myokymia—a Presumed Manifestation of Coronavirus Disease 2019 (COVID-19)

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Abstract

The purpose of this study is to report eyelid myokymia in patients recently recovered from COVID-19 disease. A cohort of 15 patients who developed eyelid myokymia during or immediate post-recovery of systemic disease were evaluated. Demographic, clinical characteristics, effect of age, and hospitalization on the disease course were studied. The disease course was evaluated every month for 3 months period. All, except 2, patients had complete resolution of lid myokymia within 3 months of onset. Median [IQR] myokymia recovery time was 42 [31,60] days. Age and duration of hospitalization had a significant linear relationship with myokymia recovery time. Recovery was delayed by 2.64 days with every 1-year increment in age and by 6.19 days with every additional day of hospital stay. Recovery time was independent of severity of systemic disease ($P = .055$) and gender ($P = 0.2$). Eyelid myokymia can be a possible manifestation of COVID-19 recovery phase. While myokymia recovers gradually in all these patients, older age and a longer duration of hospitalization are associated with slower recovery.

Keywords COVID-19 · Eyelid myokymia · Coronavirus · Blepharospasm

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Introduction

Coronavirus disease 2019 (COVID-19) is the spectrum of clinical manifestations caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is a member of Coronaviridae family [1]. The rapid transmission of the virus has caused a global pandemic with 91.8 million cases and 1.97 million deaths globally [2]. While respiratory disease caused by this virus has been most emphasized, the virus may also affect other body systems and functions.

Several investigators have described ocular manifestations of SARS-CoV-2. While ocular surface diseases are the most common ophthalmic manifestation of this virus, retinal vascular changes, neuro-ophthalmological complication, and uveal inflammation has also been seen in a small number of patients [3–5].

Eyelid myokymia is the most common type of facial myokymias seen in otherwise healthy individuals. It is a self-limiting benign condition seen as involuntary, fine, continuous, undulating contractions of orbicularis oculi muscles and may be associated with anxiety, depression, heavy caffeine intake, and drugs [6–8]. We recently encountered a higher number of patients suffering from eyelid myokymia during

the recovery phase of systemic COVID-19. The increased incidence of eyelid myokymia can be possibly related to multiple etiologies in these patients, including stress and anxiety, lack of sleep, or perhaps altered neuromusculature of eyelids. Nonetheless, no reports of COVID-19 patients experiencing eyelid myokymia have yet been published in the literature. The objective of our study is to describe features of lid myokymia developed during or immediately after the recovery from systemic disease.

Methods

In this multicenter prospective study, a cohort of patients who presented with self-reported eyelid twitching during or within 1 month of recovery from COVID-19 were recruited from 3 centers over 3 months using a convenient sampling strategy. The course and pattern of eyelid twitching were studied over 3 months. Inclusion criteria were (1) new-onset eyelid twitching noticed by patients during or immediately after COVID-19 infection, (2) age between 18 and 70 years, (3) history of recent COVID-19 infection confirmed with real-time (RT) polymerase chain reaction (PCR) for SARS-CoV-2, (4) complete recovery from active systemic infection documented by treating physician using RT PCR test negative for SARS-CoV-2 not earlier than 1 month. We excluded the patient who had (1) history of eyelid twitching within the past 1 year, (2) history of ocular surgery or trauma within the past 1 year, (3) family history of essential blepharospasm or hemifacial spasm, (4) active ocular disease including glaucoma, uveitis or ocular surface diseases, except acute conjunctivitis during systemic COVID-19 infection, (5) history of head/ face trauma of any known neurological disease, (6) current smoking, caffeine intake, alcohol consumption or current drugs known to cause eyelid myokymia including gold salts, flunarizine or antipsychotics, and topiramate.

Each patient was evaluated at baseline and every month for 3 months. Comprehensive ophthalmic and neurological assessments, including complete cranial nerve assessments, were performed at each visit, while neuroimaging was performed at baseline. Magnetic resonance imaging (MRI) of the brain was obtained at baseline for each participant.

Eyelid myokymia was defined as episodic or persistent fine, spontaneous undulating contraction involving any upper or lower lids reported by the patient and noticed during clinical examination. The condition was differentiated from fascial myokymia, spastic-paretic facial contracture, blepharospasm, facial neuromyotonia, palpebromandibular synkinesia, and facial motor seizures as described elsewhere [8–10]. The rate of occurrence was subjectively reported by the patient and graded as (1) most of the time, (2) half of the time, (3) sometimes, or (4) none of the time. Resolution of lid myokymia was defined as the patient-reported complete

absence of lid twitch for 2 consecutive weeks and absence of myokymia on clinical examination. Myokymia recovery time was the interval between the systemic disease recovery and complete resolution of myokymia.

Data Analysis

Microsoft Excel was used for data collection and handling, while statistical analysis was performed using SPSS software version 21. Data were presented as mean \pm SD or median [IQR] for quantitative variables and counts (percentages) for categorical variables. The Shapiro–Wilk test was used to analyze the normal distribution of data. All time intervals were calculated from the date of discharge from the hospital or documented recovery of systemic infection. The effect of gender and whether or not a patient was hospitalized on ocular recovery interval was tested. The relationship between the length of hospital stay, age, and ocular recovery time was analyzed using linear regression. *P* values of <0.05 were considered statistically significant.

Results

A total of 15 patients, 9 (60%) males, were evaluated over the 3 months study period. Mean \pm SD age was 48.3 ± 7.9 (range 38 to 62) years. There was no difference in age between males and females ($P=0.81$). Ten (66.7%) patients, 3 females and 7 males, had a history of hospital admission for management of COVID 19 disease. Based on WHO working groups' severity scale of COVID-19, 15 patients, 5 (33.3%) with mild disease were not hospitalized, whereas 8 (53.3) with moderate and 2 (13.3%) with severe disease were admitted to the hospital [11]. Six (40%) of the 8 patients with moderate illness required supplemental oxygen through masks or nasal prongs, while 2 (13.3%) did not. Non-invasive ventilation was used to provide high flow O₂ to both patients with severe illness. The median [IQR] duration of hospital stay was 4 [0, 4.5] days. Patients with severe disease had longer median [IQR] stay durations 10 [8.5, 11.5] days compared to mild disease 0 [0,0] and moderate disease 5.5 [4, 8] days $H(2)=10.57, P=0.005$. Systemic disease was treated with different antibiotics. Eight (53%) of patients with history of hospital admission had also received systemic dexamethasone. Five (33.3%) patients had a history of conjunctivitis during active systemic disease. All patients experienced lid myokymia, limited to orbicularis oculi muscles, during or immediately after the systemic disease recovery. Median time between systemic recovery and myokymia onset was $-2 [-4.5, 4.5]$ days. None of them had any neurological signs/symptoms during or before the current study. Interval between systemic disease recovery and baseline ocular examination was 11 [10, 16.5] days.

Patient demographics and clinical characteristics are shown in Table 1.

At baseline, 3 (20%) patients had occasional lid myokymia, 6 (40%) patients had it half the time, and the remaining 6 patients (40%) had it the most of the time. Occasional myokymia was present in 9 (60%) patients at 1-month follow-up and no myokymia in 11 (73.3%) at 2-month follow-up. At the final visit, 13 (87.7%) had complete resolution while 2 (13.3%) had been experiencing myokymia most of

the time. Figure 1 shows the disease course in the current study.

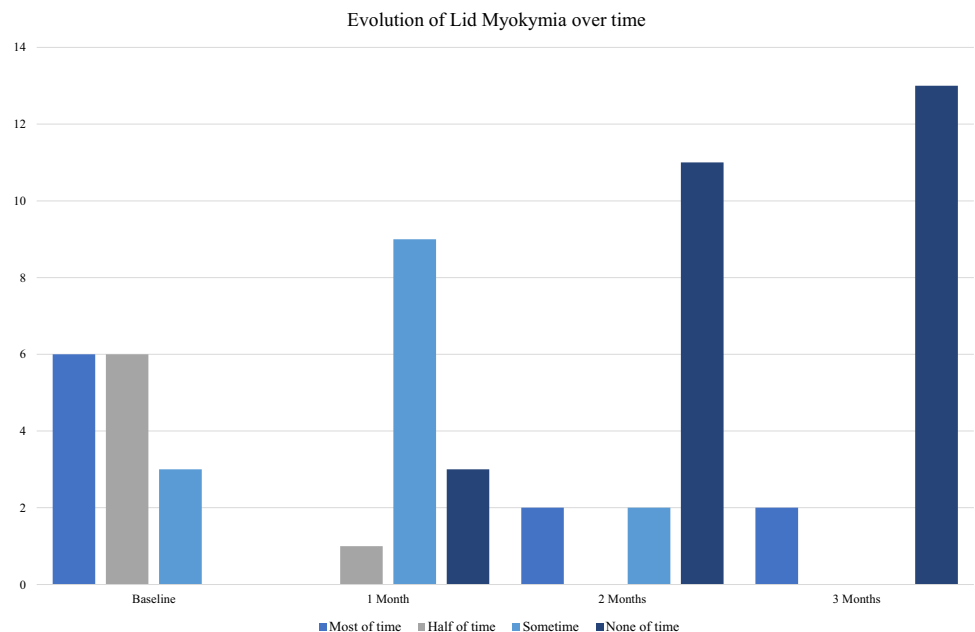
Complete recovery of lid myokymia was observed in 13 (87%) patients at 3 months post-COVID-19 recovery. The interval between systemic disease recovery and total resolution of lid myokymia was 42 [31–60] days. Two patients, each with moderate and severe disease, did not report any improvement or deterioration of twitch at 3 months. Magnetic resonance imaging of the brain in those patients was

Table 1 Patient demographics, clinical characteristics, and myokymia recovery time

Patient	Age/sex	Hospitalized/days	COVID severity score	Myokymia onset interval	Interval**	Conjunctivitis	Recovery time Days
1	38/M	Yes/3	Mod/4	3	19	Yes	31
2	44/F	Yes/4	Mod/5	-2	17	Yes	60
3	41/F	No/0	Mild/2	4	11	Yes	21
4	42/F	No/0	Mild/3	-5	10	Yes	33
5	62/M	Yes/13	Severe/6	-6	10	No	Didn't recover*
6	61/F	Yes/7	Severe/6	-3	15	No	Didn't recover*
7	46/M	Yes/6	Mod/5	-3	21	No	49
8	47/M	Yes/5	Mod/5	5	11	No	42
9	53/M	Yes/8	Mod/4	-6	8	No	88
10	55/M	Yes/9	Mod/5	-6	7	No	62
11	57/M	Yes/8	Mod/5	-4	18	No	67
12	51/M	No/0	Mild/3	8	15	No	43
13	40/F	No/0	Mild/2	3	16	Yes	18
14	49/F	Yes/4	Mod/5	7	10	No	40
15	39/M	No/0	Mod/2	5	8	No	19

*Did not recover till the end point of current study. ** Interval (days) between systemic disease recovery and baseline ocular exam. Myokymia onset interval is number of days between onset of myokymia and recovery from systemic disease (a-sign indicates number of days before recovery from systemic disease)

Fig. 1 The myokymia pattern and course



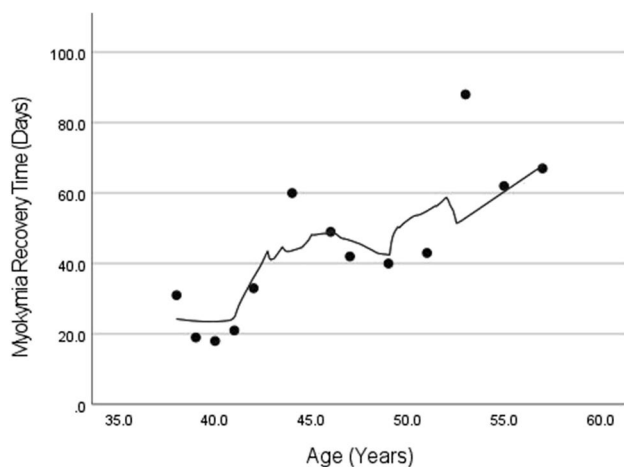


Fig. 2 Relationship between age and myokymia recovery time

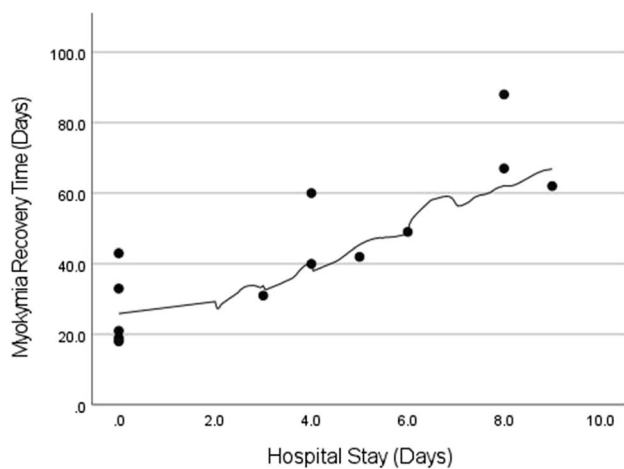


Fig. 3 Effect of length of hospital stay on myokymia recovery time

unremarkable. Myokymia recovery interval was independent of the history of conjunctivitis ($P=0.45$) and gender ($P=0.2$). The median myokymia recovery time was longer in patients with severe disease 62 [62,62] days compared to those with moderate 16 [10.75, 18.25] and mild disease 11 [10, 12] days but the difference was not statistically significant $H(2)=5.8$, $P=0.006$.

A significant regression equation was found between age and recovery time [$F(1,11)=19.74$, $P<0.001$] with an R^2 of 0.64 and a regression coefficient of 2.64 days/year (95 CI 1.33 to 3.95, $P<0.001$). Likewise, the linear relationship between duration of hospital stay and recovery time was [$F(1,6)=8.4$, $P<0.03$], $R^2=0.58$, and beta coefficient of 6.19 days/day (95 CI 0.9 to 11.48) of hospital stay.

Figures 2 and 3 show the impact of age and duration of hospitalization on ocular recovery time.

Discussion

We studied a cohort of 15 patients who experienced eyelid myokymia during the recovery phase of systemic illness. Initially, most patients had myokymia half of the time or most of the time that gradually improved to occasional myokymia and complete resolution within 3 months. Most patients had moderate disease and were administered supplemental O₂ through a mask or nasal prong. Interestingly, myokymia recovery time was independent of the severity of the systemic illness but was significantly delayed in older patients and prolonged hospitalization. Clinical neurological assessment and neuroimaging did not reveal any neurological origin of myokymia in any of our patients and all cases exhibited a classic myokymia pattern.

The primary outcome of the present study was to evaluate the pattern of eyelid myokymia presumably associated with COVID-19 and to the best of our knowledge, it is the first study reporting eyelid myokymia as a potential association of SARS-CoV-2 infection. We included all patients who experienced lid twitching during or after recovery from COVID-19 infection.

The frequency/rate of myokymia gradually declined to complete resolution and most patients fully recovered within 3 months of recovery from systemic disease. Older age and longer hospital stay were associated with prolongation of lid myokymia, while the history of conjunctivitis had no impact on the time for recovery of myokymia. Akin to classic eyelid myokymia, there was a gradual recovery of myokymia in our patients, while older age and hospitalization were associated with slower resolution of the disease.

Common ocular complications/manifestations of COVID-19 include dry eye, non-specific conjunctivitis, and retinal vascular changes. The exact incidence of these complications is yet to be determined. However, ocular surface disorders, including conjunctivitis and dry eye, are most frequently reported in COVID-19 patients [3, 5, 13, 14]. Non-specific conjunctivitis, including conjunctival hyperemia, lacrimation, follicular conjunctivitis, and ocular pain, have been reported in 5 to 31% of patients [12, 15–17], while ocular surface diseases ranging from conjunctivitis to keratopathy was seen in up to 60% of critically ill patients [18, 19]. Other relatively common ocular manifestations of SARS-CoV-2 include keratoconjunctivitis, epithelial defects, subepithelial infiltrates, and pseudodendrites [14, 20, 21].

Granulomatous anterior uveitis, retinal detachment, retinal vasculitis, retinitis, and retinal degenerations are seen in animal studies [4, 5, 14]. In a study of 54 COVID-19 patients, dilatation of retinal veins and vascular tortuosity were most common and seen in 27.7% and 12.9%

of patients. Other changes included retinal hemorrhages in 9.25% and cotton wool spots in 7.4% of patients [20]. Another study reported hyperreflective foci in the macula of 12 COVID-19 patients using optical coherence tomography. Besides OCT findings, 4 patients had cotton wool spots and retinal microhemorrhages [21]. Concerns about the potential misinterpretation of these results have recently been posed, signifying that hyperreflective areas could merely represent normal retinal vessels [22, 23]. Retinal vein occlusion and Valsalva retinopathy are rare potential associations of COVID-19 [15]. Neuro-ophthalmological associations of SARS-CoV-2 are rare. A limited number of case reports have described Miller Fisher syndrome, Guillain-Barré syndrome, polyneuritis cranialis, internuclear ophthalmoparesis, and oculomotor palsy [5]. Meningitis, encephalomyelitis, and encephalopathy may also affect these patients [14, 24]. However, eyelid myokymia in COVID-19 patients has never been reported during active illness or after recovery.

Eyelid myokymia results from doublets or triplets of spontaneous non-synchronous discharges of adjacent motor units at a 30 to 70 Hz rate with inter-discharge intervals of 100–200 ms [8, 25]. It is most common of all facial myokymias, typically unilateral with a tendency for lower lid and limited to orbicularis oculi muscle. It is a self-limiting benign condition affecting otherwise healthy individuals at any age and resolves completely over days to months [6, 8, 26]. Nonetheless, stress, anxiety, excessive caffeine intake, and administration of antipsychotics, flunarizine, gold salts, and topiramate are known associations [7, 8, 27]. Rarely, it may be associated with Guillain-Barre syndrome and multiple sclerosis [28, 29]. Eyelid myokymia in our study may be attributed to various etiologies including anxiety and stress due to COVID-19 and altered neuromuscular status of orbicularis oculi muscles. Mental illness including anxiety and depression are common, affecting roughly 1/4th to half of the COVID-19 survivors immediate post-recovery and may persist for long. The incidence of mental illness was greater in hospitalized patients [1, 30–33]. None of our patients had a recent history of topiramate, flunarizine, or other antipsychotics, intake, or heavy caffeine/alcohol consumption. Given the onset of symptoms during the recovery phase and a positive relationship between the hospitalization and ocular recovery time, mental illness appears to be the most causative factor. It can, however, be a late manifestation of COVID-19 itself. Nonetheless, given certain limitations, these results should be interpreted cautiously. First, anxiety levels were not assessed and thus it is difficult to establish a causal relationship between lid myokymia and levels of COVID-19-related anxiety. Secondly, only patients with post-COVID-19 eyelid myokymia were recruited; the incidence of lid myokymia cannot be estimated from our results. A small sample was available for study thus reducing

statistical power. In addition, we did not compare the pattern of myokymia in non-COVID-19 individuals in our study as it would not add any further helpful information.

Conclusion

Our study reports eyelid myokymia as a possible manifestation of the recovery phase of COVID 19 with clinical features identical to classic myokymia. Older age and duration of hospital stay were associated with slower recovery of lid myokymia in our study.

Author Contributions All listed authors meet ICMJE criteria for authorship. HAK, MAS, and FI were involved in the conceptualization, literature search, and drafting of the manuscript. All except FI collected data. The final manuscript was reviewed and corrected by all of the authors.

Data Availability All collected data have been presented in text and table.

Code Availability Not applicable.

Declarations

Ethics Approval The ethical approval for the study was granted by ethics committees at SEHHAT Foundation Hospital and Poonch Medical College, and the study adhered to tenets of the declaration of Helsinki.

Consent for Publication All study participants consented to publish their data for publication.

Conflict of Interest The authors declare no competing interests.

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