



Abnormal quantitative pupillary light responses following COVID-19

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Abstract

Purpose To characterize alterations in pupillary light reflex responses in subjects following coronavirus disease 2019 (COVID-19), especially those with long-COVID.

Methods Thirty-five subjects with previous COVID-19 and 30 healthy control participants were enrolled in this cross-sectional comparative study. An infrared dynamic pupillometry system (MonPack One; Metrovision, France) was used to quantify pupillary light responses. The National Institute for Health and Care Excellence (NICE) long-COVID questionnaire was used to identify persisting symptoms at least 4 weeks after acute COVID-19.

Results The median time after the diagnosis of acute COVID-19 was 4.0 (2.0–5.0) months. There was an increase in the latency of pupil contraction ($P=0.001$) and a reduction in the duration of pupil contraction ($P=0.039$) in post-COVID-19 subjects compared to healthy controls. No significant differences were observed in the initial pupil diameter, amplitude and velocity of pupil contraction or latency, velocity and duration of pupil dilation. Long-COVID was present in 25/35 (71%) subjects and their duration of pupil contraction was reduced compared to subjects without long-COVID ($P=0.009$). The NICE long-COVID questionnaire total score ($\rho=-0.507$; $P=0.002$) and neurological score ($\rho=-0.412$; $P=0.014$) correlated with the duration of pupil contraction and the total score correlated with the latency of dilation ($\rho=-0.352$; $P=0.038$).

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Conclusion Dynamic pupillometry reveals significant alterations in contractile pupillary light responses, indicative of parasympathetic dysfunction after COVID-19.

Keywords Autonomic dysfunction · COVID-19 · Dynamic pupillometry · Long-COVID · Pupillary light reflex

Introduction

During the acute phase of coronavirus disease 2019 (COVID-19), neurological manifestations involving the peripheral, central, and autonomic nervous systems have been reported, and in a proportion of patients, these symptoms and signs have been shown to persist following recovery [1, 2]. A guideline has been developed by the National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), and Royal College of General Practitioners (RCGP) for the diagnosis and management of long-COVID, defined as ‘signs and symptoms that develop during or following an infection consistent with COVID-19 and which continue for more than 4 weeks and are not explained by an alternative diagnosis’ [3]. It has been suggested that small fiber neuropathy may contribute to long-COVID [4], and we have recently demonstrated corneal nerve fiber loss in subjects with long-COVID [5].

Symptomatic autonomic neuropathy characterized by orthostatic hypotension, resting tachycardia, excessive sweating, erectile dysfunction and deficiency in ciliary accommodation has been reported in patients with COVID-19 [6–8]. Autonomic dysfunction has been confirmed with reports of impaired sudomotor function and abnormal heart rate variability in post-COVID-19 patients [9, 10].

Dynamic pupillometry can provide detailed quantification of pupillary light responses to assess dysautonomia in Alzheimer’s disease, Fabry disease, diabetes mellitus and multiple sclerosis [11–15]. We have utilized dynamic pupillometry to quantify pupillary light reflex responses and their association with long-COVID.

Materials and methods

Thirty-five subjects who had recovered from COVID-19 and 30 healthy control participants were included in this cross-sectional study undertaken at a university hospital. The study followed the principles of the Declaration of Helsinki and was approved by the Research Ethics Committee of the Necmettin Erbakan University. After detailed explanation of the study protocol, written informed consent was obtained from all participants. The diagnosis of COVID-19 infection was confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) assay of oropharyngeal and nasopharyngeal swabs. Exclusion criteria included diabetes mellitus or any other systemic disease that might cause autonomic neuropathy, a history of ocular surgery or trauma, and use of any topical or systemic medications that might influence pupillary responses. The long-COVID questionnaire developed by NICE, SIGN and the RCGP was used to identify ongoing symptoms more than 4 weeks after acute COVID-19 [5, 16]. This questionnaire comprises 28 items in nine domains (generalized, respiratory, neurological, cardiovascular, musculoskeletal, gastrointestinal, dermatological, psychological/psychiatric, and ear, nose and throat symptoms), with a total score ranging between 0 and 28. The neurological domain of this questionnaire consists of seven items, scoring from 0 to 7. Additionally, the Fibromyalgia Questionnaire (FM-Q) was used to identify additional symptoms including muscle pain and overlapping symptoms including headache, fatigue, depression/anxiety, irritable bowel, heartburn, bladder problems, waking up unrefreshed and cognitive issues, with a total score ranging between 0 and 26 [17].

Quantitative pupillary light reflex measurements were undertaken using an infrared dynamic pupillometry system (MonPack One; Metrovision, France). Dynamic pupillary responses were elicited with white light flashes (light intensity 100 cd/m², on/off time 200/3300 ms) and recorded with an infrared camera under near-infrared illumination (880 nm), which allows pupil parameters to be measured in complete darkness. Automated real-time image processing was performed, and pupil contours were outlined by the proprietary software of the device, with a measurement sensitivity of 0.01 mm. At least ten measurements were performed binocularly and the average values of the following eight parameters were

automatically quantified: initial pupil diameter (mm), amplitude of pupil contraction (mm), duration of pupil contraction (ms), latency of pupil contraction (ms), velocity of pupil contraction (mm/s), latency of pupil dilation (ms), velocity of pupil dilation (mm/s), and duration of pupil dilation (ms) (Fig. 1). For all participants, the data obtained from the right eyes were included in the analyses.

Statistical analyses were performed with SPSS 21.0 (SPSS for Windows, USA) software. Basic descriptive statistics were reported as the mean \pm SD or median (interquartile range [IQR]), as appropriate. Normal distribution of continuous variables was confirmed with the Shapiro–Wilk test. Categorical parameters were compared using the Pearson χ^2 test. Independent samples *t* test or Mann–Whitney *U* test was used to compare parameters between post-COVID-19 patients and control participants. Kruskal–Wallis test followed by Dunn’s test with adjusted *P* values using Benjamini–Hochberg procedure or one-way ANOVA test followed by Tukey multiple comparison test were used to compare the parameters among the created subgroups. The associations between study variables were measured using Pearson’s correlation coefficient for parametric data and Spearman’s correlation coefficient for non-parametric data. For all evaluations, a two-sided *P* value of less than 0.05 was considered statistically significant.

Results

The mean age of post-COVID-19 subjects was 43.7 ± 11.5 years compared to 41.2 ± 9.6 years in the control group. No significant differences were observed between the two groups for age ($P=0.353$) and gender ($P=0.565$). The median (IQR) time from the diagnosis of acute COVID-19 was 4.0 (2.0–5.0) months. The median (IQR) values of the NICE questionnaire total and neurological scores, and FM-Q score beyond 4 weeks after acute infection were 3.0 (0–6.0), 0 (0–2.0), and 5.0 (2.0–10.0), respectively. During the acute phase of COVID-19, 21 subjects (60%) had no clinical signs of pneumonia, 10 (29%) had clinical signs of pneumonia not requiring oxygen support, 3 (9%) were hospitalized and received oxygen therapy, and 1 (3%) patient was admitted to the intensive care unit for the need of respiratory support.

Compared to controls, post-COVID-19 subjects had a longer latency ($P=0.001$) and shorter duration ($P=0.039$) of pupil contraction, with no significant difference in the initial pupil diameter, velocity and amplitude of pupil contraction, and latency, velocity and duration of pupil dilation (Table 1). At least one persisting symptom was present in 25/35 (71%) subjects, beyond 4 weeks after acute COVID-19 (defined as long-COVID). Subjects with and without long-COVID had longer latency of pupil contraction when compared to healthy controls ($P=0.012$ and $P=0.010$, respectively), but did not differ between subjects with and without long-COVID. However, the duration of pupil contraction was lower in subjects with compared to without long-COVID ($P=0.009$) and healthy controls ($P=0.005$). The latency of

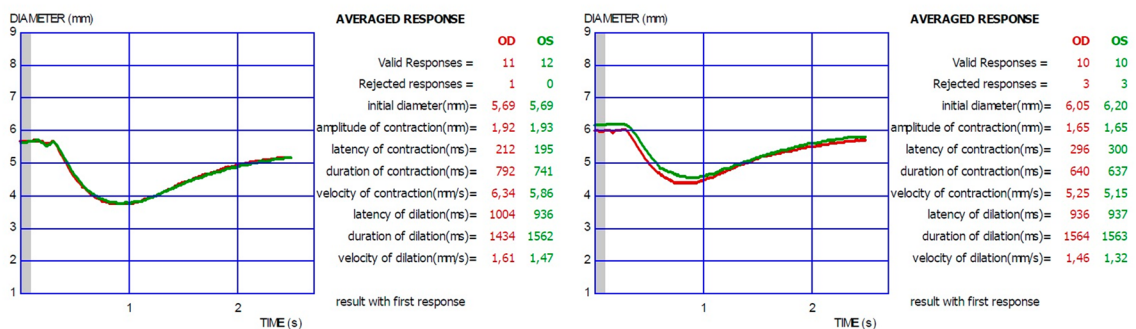


Fig. 1 Pupillary light reflex responses measured with dynamic pupillometry in a control participant (left), and a post-COVID-19 subject (right)

Table 1 Dynamic pupillary light responses in post-COVID-19 subjects and healthy controls

	Healthy controls (<i>n</i> = 30)	Post-COVID subjects (<i>n</i> = 35)	<i>P</i> value
Initial pupil diameter (mm)	5.66 ± 0.84	5.62 ± 0.88	0.873 ^a
Amplitude of contraction (mm)	1.83 ± 0.29	1.75 ± 0.34	0.265 ^a
Latency of contraction (ms)	258.0 (234.8–276.5)	285.0 (273.0–307.0)	0.001^b
Duration of contraction (ms)	662.3 ± 89.2	614.2 ± 93.5	0.039^a
Velocity of contraction (mm/s)	5.67 ± 0.94	5.48 ± 0.98	0.432 ^a
Latency of dilation (ms)	911.4 ± 80.0	892.5 ± 96.0	0.395 ^a
Duration of dilation (ms)	1575.6 ± 86.3	1575.9 ± 105.4	0.991 ^a
Velocity of dilation (mm/s)	1.69 (1.52–1.84)	1.58 (1.30–1.74)	0.092 ^b

Data are expressed as mean ± SD for parametric variables and median (IQR) for non-parametric variables. The bold *P* values represent statistically significant differences

^aIndependent samples *t* test, ^bMann Whitney *U* test

pupil dilation was also reduced in subjects with long-COVID compared to those without long-COVID (*P* = 0.014) (Table 2).

Sixteen of 35 subjects (46%) had at least one persisting neurological symptom beyond 4 weeks after

acute COVID-19. The latency of pupil contraction was longer in subjects with and without persisting neurological symptoms compared to healthy controls (*P* = 0.016 and *P* = 0.010, respectively), but did not differ between subjects with and without neurological

Table 2 Dynamic pupillary light responses in healthy control participants and post-COVID-19 subjects with and without long-COVID

	Healthy controls (<i>n</i> = 30)	With long-COVID (<i>n</i> = 25)	Without long-COVID (<i>n</i> = 10)	<i>P</i> values		
				With long-COVID versus control	Without long-COVID versus control	With versus without long-COVID
Initial pupil diameter (mm)	5.66 ± 0.84	5.62 ± 0.91	5.64 ± 0.82	0.985 ^a	0.997 ^a	0.998 ^a
Amplitude of contraction (mm)	1.83 ± 0.29	1.75 ± 0.35	1.72 ± 0.34	0.625 ^a	0.616 ^a	0.967 ^a
Latency of contraction (ms)	258.0 (234.8–276.5)	282.0 (272.0–296.5)	307.5 (246.3–317.8)	0.012^b	0.010^b	> 0.999 ^b
Duration of contraction (ms)	662.3 ± 89.2	585.9 ± 83.1	684.9 ± 82.5	0.005^a	0.753 ^a	0.009^a
Velocity of contraction (mm/s)	5.67 ± 0.94	5.66 ± 1.00	5.03 ± 0.79	0.999 ^a	0.162 ^a	0.185 ^a
Latency of dilation (ms)	911.4 ± 80.0	866.4 ± 77.9	957.8 ± 109.5	0.126 ^a	0.294 ^a	0.014^a
Duration of dilation (ms)	1575.6 ± 86.3	1593.9 ± 101.6	1530.8 ± 105.9	0.759 ^a	0.409 ^a	0.189 ^a
Velocity of dilation (mm/s)	1.69 (1.52–1.84)	1.62 (1.46–1.76)	1.37 (1.24–1.66)	0.085 ^{b*}		

Data are expressed as mean ± SD for parametric variables and median (IQR) for non-parametric variables. The bold *P* values represent statistically significant differences

*Pairwise comparisons were not performed as the overall test did not show a significant difference among groups

^aOne-Way ANOVA test followed by post-hoc Tukey test, ^bKruskal–Wallis test followed by post-hoc Dunn's test with adjusted *P* values using Benjamini–Hochberg procedure

symptoms. The duration of pupil contraction was lower in subjects with neurological symptoms compared to controls ($P=0.008$) (Table 3).

The total score on the NICE questionnaire correlated with the duration of contraction ($\rho=-0.507$; $P=0.002$) and latency of pupillary dilation ($\rho=-0.352$; $P=0.038$). The neurological score on the NICE questionnaire and FM-Q correlated with the duration of contraction ($\rho=-0.412$; $P=0.014$ and $\rho=-0.488$; $P=0.003$, respectively).

Discussion

This study shows evidence of increased latency and reduced duration of pupil contraction, indicative of parasympathetic dysfunction in subjects who have recovered from mild COVID-19. Furthermore, the severity of pupillary dysfunction was related to the number of persisting symptoms assessed by the

NICE long-COVID questionnaire and FM-Q. These abnormalities are consistent with a growing body of literature suggesting that COVID-19 may be associated with autonomic dysfunction. Ghosh et al. [6] reported postural hypotension, constipation, intermittent profuse sweating and erectile dysfunction, preceding an acute motor axonal neuropathy in a patient with acute COVID-19. Umaphathi et al. [7] described patients with acute COVID-19 who developed hyperhidrosis, orthostatic tachycardia and impaired pupillary accommodation. Abnormalities in quantitative sudomotor axon reflex testing, thermoregulatory sweat test, electrochemical skin conductance, and cardiovascular autonomic testing have been described in post-COVID-19 patients [9, 10, 18–21]. In a recent study by Shouman et al. [18], abnormalities in autonomic function tests were detected in 63% of patients during or after COVID-19, with the most common finding being orthostatic intolerance. The Composite Autonomic Symptom

Table 3 Dynamic pupillary light responses in healthy control participants and post-COVID-19 subjects with and without neurological symptoms at 4 weeks

	Healthy controls ($n=30$)	With neurological symptoms at 4 weeks ($n=16$)	Without neurological symptoms at 4 weeks ($n=19$)	<i>P</i> values		
				With neurological symptoms versus control	Without neurological symptoms versus control	With versus without neurological symptoms
Initial pupil diameter (mm)	5.66 ± 0.84	5.58 ± 0.78	5.66 ± 0.97	0.955 ^a	0.999 ^a	0.961 ^a
Amplitude of contraction (mm)	1.83 ± 0.29	1.71 ± 0.30	1.78 ± 0.37	0.414 ^a	0.812 ^a	0.803 ^a
Latency of contraction (ms)	258.0 (234.8–276.5)	285.5 (266.8–300.5)	283.0 (273.0–311.0)	0.016^b	0.010^b	> 0.999 ^b
Duration of contraction (ms)	662.3 ± 89.2	576.8 ± 81.2	645.7 ± 93.4	0.008^a	0.800 ^a	0.064 ^a
Velocity of contraction (mm/s)	5.67 ± 0.94	5.59 ± 0.92	5.38 ± 1.04	0.965 ^a	0.577 ^a	0.801 ^a
Latency of dilation (ms)	911.4 ± 80.0	861.5 ± 76.0	918.6 ± 105.0	0.162 ^a	0.958 ^a	0.139 ^a
Duration of dilation (ms)	1575.6 ± 86.3	1602.4 ± 97.8	1553.5 ± 108.8	0.641 ^a	0.715 ^a	0.298 ^a
Velocity of dilation (mm/s)	1.69 (1.52–1.84)	1.58 (1.46–1.76)	1.59 (1.27–1.64)	0.172 ^{b*}		

Data are expressed as mean ± SD for parametric variables and median (IQR) for non-parametric variables. The bold *P* values represent statistically significant differences

*Pairwise comparisons were not performed as the overall test did not show a significant difference among groups

^aOne-way ANOVA test followed by post-hoc Tukey test, ^bKruskal–Wallis test followed by post-hoc Dunn's test with adjusted *P* values using Benjamini–Hochberg procedure

Scale 31 (COMPASS-31) questionnaire identified orthostatic intolerance, gastrointestinal, secretomotor and pupillomotor dysfunction in a cohort of 180 subjects with previous COVID-19 [22].

Quantitative evaluation of the pupillary light reflex enables relatively rapid evaluation of sympathetic and parasympathetic dysfunction. We have previously demonstrated a reduction in the amplitude and duration of pupillary contraction and latency of pupillary dilation in relation to the severity of autonomic symptoms based on the COMPASS 31 questionnaire in patients with Fabry disease [15]. Karahan et al. [23] reported an increase in resting pupil diameter as well as alterations in static and dynamic pupil parameters in subjects 1 month after COVID-19; but did not relate them to ongoing symptoms or presence of long-COVID. Abnormalities in accommodation, tonic pupil and the Holmes-Adie syndrome have also been described in people with COVID-19 [7, 24–26]. Vrettou et al. [27] hypothesized that the increase in pupil size and reduced pupillary light response in patients with COVID-19 may be an acute phenomenon with cytokine activation of the locus coeruleus and inhibitory signaling to the Edinger–Westphal nucleus. However, we now show altered pupillary responses, 4.0 months after acute COVID-19 characterized by a prolonged latency and a shorter duration of pupil contraction indicative of continuing parasympathetic dysfunction. Our findings could be attributed to the development of small fiber neuropathy associated with COVID-19 [4, 28–30]. Of note a possible ocular neurotropism has been hypothesized for SARS-CoV-2 [31–33]. We have recently shown a loss of corneal sub-basal nerve fibers, which are predominantly sensory but also contain autonomic nerves, and related it to the severity of long-COVID [5]. Long-COVID is defined as the persistence of symptoms at least 4 weeks after acute COVID-19 and post-COVID-19 syndrome when symptoms persist more than 12 weeks after acute infection [16]. Charfeddine et al. [34] suggested that long-COVID symptoms may be associated with an abnormal microcirculation and endothelial dysfunction and of course microvascular alterations may play a role in the pathogenesis of nerve damage [35]. Further investigation is needed to assess the role of microcirculatory dysfunction in the pathophysiology of altered pupillary responses in long-COVID.

A limitation of our study was the lack of a specific autonomic symptom questionnaire to assess the severity of dysautonomia. However, we used the NICE questionnaire and FM-Q to evaluate symptoms which evaluate some aspects of autonomic dysfunction. This study also assessed a relatively small sample size, and the cross-sectional study design precludes causal inferences.

In conclusion, we have utilized dynamic pupillometry to demonstrate predominantly parasympathetic pupillary dysfunction in post-COVID-19 patients. Dynamic pupillometry is relatively easy to perform and could be used to rapidly screen for autonomic dysfunction in patients with long-COVID.

Author contributions GB, CK, and RAM contributed to the conception and design of the study; GB, CK, AZ, HK and RAM contributed to acquisition and analysis of data; MSI performed statistical analyses; GB and CK contributed to drafting the text and preparing the figures; AZ, MSI, HK and RAM reviewed the draft, provided suggestions and improvements.

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Data availability All anonymized data that support the findings of this study are available to any qualified researcher upon reasonable request to the corresponding author (ORCID: 0000–0002–0509–5649).

Declarations

Conflict of interest The authors have no financial or proprietary interests in any material discussed in this article.

Ethics approval Approval was obtained from the ethics committee of Necmettin Erbakan University. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Consent to participate Informed consent was obtained from all individual participants included in the study.

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