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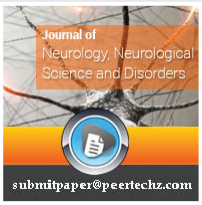

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Research Article

Blink reflex changes in patient with long COVID headache

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Abstract

Background: Headache is a common symptom of long COVID. Blink Reflex (BR) may indicate possible brainstem dysfunction or changes in excitability in the headache. In this study, we aimed to reveal whether one of the underlying mechanisms of headache in long COVID is dysfunction in the nociceptive centers in the brainstem.

Methods: The study included 29 individuals with confirmed 2019 coronavirus disease (COVID-19) and 17 healthy volunteers. Individuals were divided into 3 groups: post-COVID-19 headache (Group 1), post-COVID-19 headache-free (Group 2) and healthy individuals (Group 3). Individuals in the groups were subjected to BR and the parameters obtained with BR were compared between the 3 groups.

Results: Accordingly, when Group 1 and Group 2 were compared, the mean latency of the R1 component of the BR and the mean latency of the ipsilateral R2 component obtained via right-sided electrical stimulation were found to be longer in Group 1. When Group 1 and Group 3 were compared, the latency differences of the ipsilateral R2 component and contralateral R2 component of the BRs were found to be longer in Group 3, indicating distinct patterns of neural response between the two groups.

Conclusion: In long COVID patients experiencing headache symptoms, the underlying cause of the pain symptom may be brain stem dysfunction.

Abbreviations

COVID-19: 2019 Coronavirus Disease; BR: Blink Reflex; MIDAS: Migraine Disability Assessment Scale; VAS: The Visual Analogue Scale

Introduction

The 2019 coronavirus disease (COVID-19) has manifested a wide variety of symptoms and signs since the day it spread incredibly rapidly. Respiratory, gastrointestinal, and musculoskeletal symptoms are commonly seen, and patients also frequently suffer from neurological symptoms such as headache, dizziness, and anosmia [1-3]. "Long COVID" refers to patients who recover from COVID-19 but whose symptoms persist for much longer than expected [1,4]. 75% of COVID-19 survivors exhibit post-COVID sequelae. Studies have shown that the prevalence of headache as a symptom of Long COVID ranges from 2% to 15% [1,4]. The Blink Reflex (BR) is an objective electrophysiological method that studies the reflex responses obtained by a trigeminal nerve and assesses the function of the brain stem and subcortical structures. The afferent branch of the BR is the ophthalmic division of the trigeminal nerve and the efferent branch is the facial nerve. Ipsilateral early (R1) and bilateral late (R2) responses are obtained in the stimulated region. The R1 response involves synapses between the main sensory nucleus of the trigeminal nerve and the motor nucleus of the ipsilateral facial nerve. The entire reflex arc is located in the pons and is not associated with a clinically recognizable response. R2 responses are multisynaptic pathways mediated

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between the nuclei of the spinal tract of the trigeminal nerve and both the ipsilateral and contralateral facial nerve motor nuclei. R2 recordings can be used to assess brainstem reticular formation and excitability of corticoreticular pathways and are clinically observed as bilateral blinking. The R2 component is modulated by segmental and suprasegmental mechanisms and provides information about the excitability of brainstem interneurons and functions related to synaptic transmission at the brainstem level and is affected by abnormalities at various levels of the brain [5-7]. BR may indicate possible brain stem dysfunction or changes in excitability in headaches [8]. In the headache literature, BR studies have indeed suggested primary dysfunction of the nociceptive control center system in patients affected by TTH and cluster headaches [8-10]. In this study, we aimed to reveal whether one of the mechanisms underlying the headache symptom of long COVID is due to dysfunction in the nociceptive centers in the brainstem, based on the knowledge that coronaviruses are neurotropic viruses.

Methods

The study included 29 individuals with confirmed COVID-19 and 17 healthy volunteers who were similar in age and gender to the patient group. Ethics committee approval and informed consent of individuals were obtained for the study (E1-21-1908). Detailed evaluations of the individuals included in the study were performed in the Neurology Outpatient Clinic. None of the individuals participating in the study had a known chronic or neurological disease or continuous drug use. The Visual Analogue Scale (VAS) was used to measure the severity of pain in patients experiencing headaches. In addition, the Migraine Disability Assessment Scale (MIDAS) inventory was applied to the patients with headaches to measure disability due to headaches. Visual Analog Scale (VAS): The scale developed by Price et al. in 1983 is used to determine the severity and level of pain in the patient [11]. This scale is used to convert some values that cannot be measured numerically into numerical form. The patient marks their own pain on a 10 cm ruler, with no pain at one end and the most severe pain at the other. The test has been validated for a very long time and is widely accepted in the worldwide literature [12,13]. Migraine Disability Assessment Scale (MIDAS): MIDAS consists of five questions that assess disability due to headache throughout three activities (school or paid work; housework; family, social, and leisure activities) in the 3 months prior to its implementation. The final total score obtained with these questions categorizes disability in relation to the number of days missed doing these activities and the severity of the attacks; no or very mild disability (0-5 points), mild disability (6 - 10 points), moderate disability (11 - 20 points), or severe disability (≥ 21 points). In addition to the aforementioned five questions, the test includes two more questions that are not included in the score, but provide the clinician with important information about headache frequency (MIDAS-A) and pain intensity (MIDAS-B) in the last 3 months [14-16]. A BR study was performed on the individuals included in the study. An electroneuromyography (Keypoint 4-channel EMG device, Medtronic, Skovlunde, Denmark) device with a BR test program was used to elicit and record BR responses and to randomly repeat stimulations at various time intervals. The Kimura method was used in the BR examination [17]. The patients were placed in a quiet and warm room with their eyes slightly closed, and surface recording electrodes were placed in the lower lateral aspect of the bilateral orbicularis oculi muscle. Reference electrodes were placed on the nasal root bilaterally. The ground electrode was placed around the arm. Square wave negative single pulses lasting 0.2 ms were transmitted by a constant current isolation unit. The filter settings used were 50 - 3000 Hz, 200 µV/division sensitivity, and an analysis time of 200 ms. Ipsilateral and contralateral responses were recorded. The stimulus intensity was 0.2 ms. The nerve was stimulated randomly and without informing the patient at 20 - 30 s stimulation intervals to avoid habituation. The latencies of the R1 components and the ipsilateral and contralateral R2 components were determined. The individuals participating in the study were divided into 3 groups:

Group 1: Patients with confirmed COVID-19 infection at least 12 weeks prior, who had no prior headache history, and whose headache began with infection and persisted up to the time of electrophysiological testing.

Group 2: Individuals with confirmed COVID-19 infection during the last 12 months, who had no headache during or after infection.

Group 3: Healthy individuals with no known disease and no known COVID-19.

The data obtained were compared across Group 1, Group 2 and Group 3. The average ± standard error values were used for the variables. In addition, the homogeneity of variance, which is one of the preconditions of the parametric tests, was checked with Levene's test. The normality hypothesis was evaluated with the Shapiro–Wilk test. Because it is used to evaluate the differences between two groups, the Student's t-test was used if the parametric test preconditions were fulfilled, and the Mann–Whitney U test was used if the parametric test preconditions were not fulfilled. The relationship between the two variables was evaluated with the Kendall rank correlation coefficient if the parametric test preconditions were not fulfilled. IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). Program was used for statistical analysis and calculations. The statistical significance level was accepted as $p < 0.05$.

Results

While the mean age of Group 1 patients was 47.64 ± 10 67 years, the mean age of Group 2 patients was 44.83 ± 11.26, and the mean age of the individuals in Group 3 was 46.41 ± 8.48. 64.7% of those in Group 1 are female, 35.3% are male, 58.3% of the individuals in Group 2 are female, 41.7% are male, 41.2% of Group 3 individuals are female, and 58.8% are male. There was no significant difference between the groups in terms of age and gender ($p \geq 0.05$). The median time from the onset of symptoms of COVID-19 to the day of the test when the electrophysiological study was performed in Group 1 was 190 days, compared to 185 days in Group 2, and there was no difference between the two groups in this respect. The mean number of painful days per

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month of Group 1 individuals who developed headaches after COVID-19 was 16.4 ± 8.9. In Group 1, the mean of VAS was 6.8 ± 8.9, and the mean of MIDAS was 2.8 ± 0.1. The latency values of the R1, Ipsilateral R2, and contralateral R2 components of the BRs of the individuals in Group 1, Group 2, and Group 3 are shown in Table 1. Accordingly, when Group 1 and Group 2 were compared, the mean latency of the R1 component of the BR obtained by right-sided electrical stimulation and the mean latency of the ipsilateral R2 component was found to be significantly longer in Group 1 patients (p - value, respectively = 0.02, 0.004). When Group 2 and Group 3 were compared, no significant difference was found between the two groups in the averages of the latency and latency differences of the waves obtained using BR.

The values of the latency differences between the right and left sides of the R1, ipsilateral R2, and contralateral R2 components obtained by right and left electrical stimulation of the individuals in Group 1, Group 2, and Group 3 are displayed in Table 2. Accordingly, when Group 1 and Group 3 were compared, the latency differences of the ipsilateral R2 component and contralateral R2 component of the BRs were found to be significantly longer in the individuals in Group 1 (p values 0.02, 0.01, respectively). In Group 1, 88.2% of the ipsilateral R2 difference was within the normal range (≤ 5 msn), and 12.8% (≥ 5 msn) of it was abnormally increased. In Group 1, the R1 latency difference was within normal limits in 41.2% of individuals, while there was an abnormal increase in 58.8% of them. In Group 2, the R1 latency difference was normal in 66.7% of the individuals, while there was an abnormal increase in the other 34.3%. Other latency differences examined were within the normal range in all groups. The following data were used for normal values:

R1 (IPSYLATERAL): Latency <13 msec, latency difference between 2 sides <1.2 msec

R2 (IPSYLATERAL): Latency <41 msec, latency difference between 2 sides <5 ms

R2 (CONTROLATERAL): Latency <44 msec, 2 sides Latency difference between <7 msec

A significant and positive correlation was found between the median time from symptom onset to the time of the electrophysiological test and the right R2 component of BR obtained by right-sided electrical stimulation (p = 0.04). No correlation was found between the components of the BRs and the number of days with pain, VAS, and MIDAS of the individuals in Group 1.

Table 1: The latency values of the R1, Ipsilateral R2, and contralateral R2 components of the BRs of the individuals in Group 1, Group 2, and Group 3.

Variables	Group 1	Group 2	Group 3
R1 latency with right-side stimulation	8.9 ± 1.5	8.8 ± 0.6	8.8 ± 1.2
R1 latency with left-side stimulation	9.3 ± 1.7	8.8 ± 1.1	9.0 ± 1.1
İpsilateral R2 latency with right-side stimulation	27.1 ± 3.1	26.4 ± 1.6	25.9 ± 1.8
İpsilateral R2 latency with left-side stimulation	26.9 ± 3.1	26.1 ± 2.1	27.0 ± 2.2
Contralateral R2 latency with right-side stimulation	25.2 ± 2.8	25.9 ± 2.7	25.3 ± 1.4
Contralateral R2 latency with left-side stimulation	25.8 ± 3.1	24.5 ± 2.8	24.9 ± 1.4

Table 2: The latency differences between the right and left sides of the R1, ipsilateral R2, and contralateral R2 components of the individuals in Group 1, Group 2, and Group 3.

Variables	Group 1	Group 2	Group 3
R1 latency differences	0.5 ± 1.3	0.8 ± 0.6	0.6 ± 0.5
Ipsilateral R2 latency difference	2.0 ± 1.7	1.2 ± 0.9	2.1 ± 2.1
Contralateral R2 latency difference	0.7 ± 1.5	1.0 ± 0.8	1.4 ± 1.4

Discussion

In our study, when we compared the patients who experienced a long-term headache after COVID-19 and the patients who had COVID-19 but did not experience headache, we found the mean latency of the R1 component of the BR obtained by right-sided electrical stimulation and the latency of the ipsilateral R2 component to be long in the patient group experiencing headache. In addition, we found the latency differences of the ipsilateral R2 component and contralateral R2 component to be significantly longer in favor of the right side in patients suffering from headaches along with COVID-19.

Some studies have reported persistent headaches after viral infections [18]. In addition, the frequency of post-COVID headaches has been reported to be 2-15% [1,19-22]. According to the data obtained, it is thought that headache develops directly due to various reasons in these patients [23]. It is estimated that the underlying pathological processes of headache are the prolonged porinflammatory response and trigmnovascular overstimulation of the cytokine storm [24,25]. In addition, other factors such as altered microstructural and functional integrity of the brain or emotional distress observed in COVID-19 survivors may also contribute to the development of post-COVID headaches [1]. Our findings support the presence of brain stem dysfunction and involvement of nociceptive centers in the brain stem in these patients. Prior to the global emergence of SARS-CoV-2, other coronaviruses have been observed to cause brainstem involvement in mice and humans [26-29]. In a study, they presented neurophysiological evidence of brainstem involvement associated with BR and SARS Cov-2, especially at the medullary level, in individuals with severe respiratory failure due to COVID-19 [30]. It can be said that the R1 component latency prolongation is caused by the elongation in the stimulation threshold, changes in the R2 delay are caused by the polysynaptic transition in the brain stem including the pons, lateral medulla, and reticular formation and the excitability of interneurons, and one of the mechanisms of post-COVID-19 headache is brain stem dysfunction [5]. It is known that SARS-CoV-2 is a neurotropic virus capable of infecting and multiplying in neuronal cell cultures and murine brain cells [31-34]. In addition, autopsy studies have shown that individuals who died due to COVID-19 had SARS-CoV-2 RNA in their brain tissue [35-37]. Interestingly, some studies have supported that this involvement is particularly evident in the brainstem [38,39]. Thus, it has supported the hypothesis

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that brainstem tropism is related to SARS-CoV-2. In particular, brain autopsies demonstrated brainstem leukocyte infiltration, microglia, and astrocyte activation [31,40-42]. It is already known that the brain stem is a tissue against acute or chronic damage [31,43]. Another reason for this tropism may be the excess of ACE-2 receptors in the brain stem, which SARS-CoV-2 uses to infiltrate cells [31,44,45]. Therefore, the pathologies in the BR responses we found can be attributed to brain stem dysfunction in these patients and the same mechanisms have also been implicated in migraines or other types of chronic headaches [46-48].

However, it is an interesting finding of our study that abnormalities in BR point to right-sided brainstem dysfunction. When we examined the literature, we could not find any information regarding general dysfunction, in which BR abnormalities differed between the parties, and anatomical involvement was not determined. However, this may be the result of differences in the regeneration capacity of the sides of the brain. In addition, the length of the time from the onset of infection to the time of testing, as well as the atrophy of the R2 latency of the BR component, suggest that the dysfunction becomes more pronounced when the probability of regeneration decreases. This study is preliminary in finding that brain stem involvement may be one of the contributing factors in Long COVID. This issue must be focused on, and multi-case autopsy studies are required to reveal this.

Conclusion

Coronaviruses are neurotropic viruses and can affect the nervous system at many levels. Additionally, neuroinflammation during this infection may also be responsible for neurological findings. Headache, one of the symptoms of Long COVID, may be caused by the involvement of pain pathways in the brainstem.

Acknowledgment

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Authors contributions

SG, GV, OD, RY, and SB planned the study. SG, GV, OD, RY, and SB trained the patients and spouses. SG, GV, and RY performed neuropsychological testing. All authors contributed to the analysis and made the first draft of the manuscript and all authors have approved the final version of the manuscript.

Ethical approval and consent to participate

All the participants were able to give consent to participate in the study and signed a written consent form. The study was carried out in accordance with the Declaration of Helsinki and was approved by the Ankara City Hospital Ethics Committee.

Data availability statement

The data is not located on an open server but could be made available on request to the corresponding author.

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