A Near-Global Slowing of Background Activity and Epileptic Discharges in Children With Mild to Moderately Symptomatic COVID-19 Infection: An Electro-Neurophysiological Study

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Abstract
Background. To assess the functional involvement of the central nervous system (CNS) via quantitative electroencephalography (EEG) analysis in children with mild to moderate COVID-19 infection who were otherwise previously healthy children. Methods. This prospective, case-control study was conducted between June and September 2020. Sleep EEG records of at least 40 min were planned for children who tested positive for COVID-19 using real-time PCR analysis and within 4–6 months post-recovery. All of the EEG analyses in this study were performed on an Ubuntu 20.04.2 LTS Operating System with the developed software using Python 3.7.6. The quantitative analysis of the epileptic discharges within the EEG records was performed using random forest after elimination of the artifacts with a model training accuracy of 98% for each sample data point. The frequency analysis was performed using the Welch method. Results. Among the age and sex-matched groups, the global mean frequency was significantly lower among the COVID-19 patients, with a P-value of 0.004. The spike slow-wave and sharp slow-wave indices were significantly higher in the patients when compared to the controls. The mean frequency values were significantly lower in almost all of the electrodes recording the frontal, central, and occipital areas. For the temporal and parietal areas, those significantly low mean frequencies were limited to the right hemisphere. Conclusion. A near-global involvement of background activity with decreased frequency, in addition to epileptic discharges, was recorded in mild to moderately COVID-19 infected children post-infection.

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Introduction
Coronavirus disease 2019 (COVID-19) is caused by a highly pathogenic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that was first detected in Wuhan, China, in December 2019. Current data suggests that the disease caused by SARS-CoV-2 in children and young adults occurs in a milder form when compared to that in adults. Eighty percent of paediatric-age patients are asymptomatic or present with only mild symptoms, which include fever and coughing. There are, however, reports of severe COVID-19 in children, where the patients developed multisystem inflammatory syndrome, which necessitates admission to the intensive care unit.

Neurologically related symptoms have been linked with SARS-CoV-2 infection. The proposed mechanism, which induces the neurologically related symptoms, involves the angiotensin-converting enzyme 2 (ACE2)-direct mediated invasion pathway of the virus to the central nervous system (CNS). The link between SARS-CoV-2 infection and neurological manifestations has been strengthened via reports of SARS-CoV-2-infected patients and the onset of immune-mediated neurological syndromes, including Miller Fisher Syndrome, steroid-responsive cranial syndrome, and steroid-responsive encephalitis. Endotheliopathy caused by COVID-19 may explain how the immune system is exposed to new CNS antigens, resulting in the immune-mediated attack of the CNS. To date, neurological manifestations in SARS-CoV-2-infected patients have been best described in adult patients. In a cohort in Wuhan, 78 of 214 (36.4%) patients had neurologically related symptoms, including dizziness, headache, and impaired consciousness. Within this cohort, patients with severe infection...
had more neurological presentation. No neurological involvement was documented in a report of 171 Chinese children with COVID-19 infection. In another study, non-specific headaches were the only neurological symptoms reported among children with COVID-19 infections, and accounted for 4%–28% of the cases. As the COVID-19 pandemic continues a year after the initial outbreak there are increasing reports of COVID-19-infected patients from the paediatric age group that have presented neurological related symptoms. In a study involving 50 children with a COVID-19 infection, 27 had a multysystemic inflammatory response and a total of 4 (14.8%) patients presented with symptoms that included encephalopathy, brainstem involvement with dysarthria or dysphagia, meningism, and cerebellar ataxia. All 4 of the patients had a severe infection and circulatory shock. Of the patients, 2 had diffuse slowing, whereas 1 had mild excess slow activity over their anterior regions of the electroencephalography (EEG) record. When 6 reports comprising 187 children who were diagnosed with multisystem inflammatory syndrome were reviewed, the rate of neurological involvement was determined to be 34%. Most of the literature focusing on neurological involvement has been based on severe cases of COVID-19. Some patients with COVID-19 have been described to have symptoms similar to those of epileptic patients, as well as the sharp waves detected on the EEG records of adults. In an EEG study that included 18 adult patients who were admitted with neurological manifestations that included loss of consciousness, seizure, delirium and coma, 88.9% of the patients displayed generalized EEG slowing, while 55.6% of the patients displayed an anterior prevalence of slow waves, and 2 patients with epileptiform discharges without seizure were also documented.

In a study that evaluated the EEGs of COVID-19 patients who had confusing or delayed awakeness after cessation of sedation in the intensive care unit, 57.5% were found to be normal or mildly altered, 10% had moderate EEG abnormality, 20% had severe changes, and 12.5% had critical changes. Visual analysis was performed and the asymptomatic patients were excluded from that study, in addition to patients of older age and those who had multiple comorbidities. In another study that evaluated the EEGs of 20 COVID-19 patients who had an altered mental status, only diffuse theta and delta slowing were observed. However multiple aetiologies such as metabolic, toxic, hypoxic aetiologies can cause rhythmic delta activity and slowing. In another recent review that included 177 patients, generalized slowing and epileptiform activity were reported at a rate of 63.8% and 19.2%, respectively. In addition, electrographic seizures have been reported without clinical seizure in patients with COVID-19. No studies demonstrating EEG changes in asymptomatic or mildly symptomatic COVID-19 patients have been reported within the English literature.

The present study aimed to objectively determine the EEG findings of children after mild to moderate COVID-19 infection.

Material and Methods

This study was approved by the Ethical Review Committee of Ankara Research and Training Hospital (Ethical approval number: 549). The study was conducted in accordance with the Declaration of Helsinki.

 Patients and Definitions

Paediatric patients who were between 6 and 17 years of age, who were determined to be COVID-19-positive using real-time PCR analysis between 1 March and 1 July 2020 were invited to the Paediatric Neurology Outpatient Clinic for re-evaluation between 10 June and 1 October 2020. Thus, patients who were at least 4 and at most 6 months post-COVID-19 infection were included in the study. The age- and sex-matched control group comprised healthy children who had no prior diagnosis of epilepsy or other neurometabolic or neuroinflammatory diseases. The patient and control group participants whose legal guardians did not provide consent and those with a history of epilepsy or epileptic seizure were excluded from the study. The patient and control groups consisted of a population who lived in the same sociocultural environment and had similar economic income depending on the location of the hospital where the study was conducted.

Data regarding the age, gender, and COVID-19 infection severity of the patients were gathered from their medical files. The COVID-19-positive patients were classified according to disease severity based on clinical and laboratory data re-evaluated from the hospital records. Patients with no clinical symptoms and normal chest imaging results were classified as asymptomatic, while those who had a high fever (ie a temperature that was higher than 37.8 °C), and presented with myalgia, throat pain, coughing, or nasal discharge with normal lung auscultation findings were classified as having mild COVID-19 infection. On the other hand, patients who had a high fever, coughing, or wheezing accompanied by pneumonia, or those who had COVID-19-associated changes on their computerized chest tomography without clinical findings were classified as having moderate COVID-19 infection. Patients who had dyspnoea and low oxygen saturation (ie <92%) were classified as having severe COVID-19 infection, and those who had rapidly progressing acute respiratory distress syndrome or respiratory failure with multiple organ dysfunction were classified as critical.

All of the patients underwent initial and serial awake and sleep EEG recording using the SAM 32 EEG acquisition system (Micromed S.p.A., Mogliano Veneto, Treviso, Italy) with 18 channels and the scalp electrodes were distributed according to the 10–20 system. None of the participants were given any sedative drugs and the EEG recordings were obtained during spontaneous sleep in both groups. To be able to obtain 10 min of arousal- and artifact-free EEG epoch of phase-2 sleep, EEG recordings of a minimum duration of 40 min were performed after sleep deprivation. The timing of the
EEG recordings for the participants in the patient group was planned after 4 to 6 months of Covid-19 infection.

Initially, the spike waves, spike and slow waves, sharp waves, and sharp slow waves were detected visually by 2 senior child neurologists, and the ones that two child neurologists agreed were a discharge (spike wave, spike slow wave and sharp slow wave).

Spike waves, spike and slow waves, sharp waves, and sharp slow waves were detected using the machine learning model, and their indices were calculated as the percent of their duration of activity within the evaluated epoch time.

Quantification of EEG

Initially, the noise removal process was applied, and the heart beat, ocular, low-frequency, and power-line noise were eliminated in the electroencephalogram recordings. Then, all recordings were filtered in the frequency domain (1-63 Hz.).

Automated identification of epileptic discharges using a machine learning model requires the samples or features of a signal to be trained. These samples or features could be extracted by the time or frequency domain analysis. In this study, 4 sleep spindle, 3 sharp slow wave, 1 spike wave, and 3 spike slow wave 1-second discrete time-domain samples were determined, extracted, and confirmed by 2 medical experts among reference patients. Considering the same epileptic discharges of different patients allowed the detection of small changes of the epileptic discharges that may occur in other patient recordings and yielded the model not to be affected by the differences in the frequency obtained from patients of different ages groups or different electrodes. Moreover, 3 significant artifact samples that occurred during the acquisition were selected to be included in the analysis. Selected samples were extracted as features for each epileptic discharge to train the machine learning model. Each extracted 1-second sample provided 128 data points in the time domain for model training.

Machine learning models do not provide exact template matching, which causes misclassification because of noise and small changes in the testing samples. Their primary purpose is to provide a noise-free and flexible classification of samples by considering small changes in the samples. This flexibility allows the samples to be identified more accurately and assists experts in the fields that they are employed in.

Four machine learning models, namely random forest (RF), support vector machine (SVM), decision tree (DT), and logistic regression (LR), were trained and tested on the EEG recordings before the analysis process and compared to the results that were obtained by RF. The comparative analysis of ML models has vital importance in determining superior ML models while different models could produce optimal results for particular datasets and applications. Initial experiments were performed to create 2-class (binary) combinations of individual epileptic discharges to optimize the training process of the models. The considered models were trained using various epileptic discharges. In this study, RF achieved superior training and testing results when compared to the other models by obtaining a minimum of 96% accuracy, which was followed by SVM with 84% accuracy. Therefore, the analysis of the EEG records was performed using RF, which is an ensemble model that creates several individual decision trees and optimizes the outputs.

Based on the obtained results of the initial experiments, 4 different RF models were created, and a single epileptic discharge was trained with artifact samples, which were used commonly in the training of all of the models. This process aimed to train the models using the significantly distinguishable samples and improve the convergence of the models, leading to increased classification accuracy. The 4 created models were trained using the sleep spindle + artifact, sharp slow-wave + artifact, spike slow-wave + artifact, and spike-wave + artifact samples, respectively. Table 1 presents the details of the created RF models and the considered epileptic discharges for each model.

An iterative process was implemented in the analysis of the EEG recordings. The determination of stage 2 and the identification of epileptic discharges within the specified stage were carried out sequentially. Model 1 scanned the Cz channel of the patient recordings in the control and COVID-19 groups during the recordings and determined stage 2 by identifying the sleep spindles in the first iteration. The beginning of stage 2 was assigned as a starting time of 10 min of recordings and extracted for the other models. In the following iterations, models 2, 3, and 4 performed further analysis by considering 1-second samples over an extracted period, respectively. These completed iterations identified and determined the number of epileptic discharges, sharp slow waves, spike waves, and spike slow waves, in the EEG recordings, separately.

Finally, all of the identified samples were compared to check if any overlapped identification occurred. Although overlapped samples were rarely obtained during the analysis, the post-

| Table 1. Properties of RF Models. |
|-----------------------------------|
| Model # | Class 1 | # of training samples for Class 1 | Class 2 | # of training samples for Class 2 |
|---------|---------|---------------------------------|---------|---------------------------------|
| Model-1 | Sleep Spindle | 3 | Artifact | 3 |
| Model-2 | Sharp Slow Wave | 3 | Artifact | 3 |
| Model-3 | Spike Slow Wave | 3 | Artifact | 3 |
| Model-4 | Spike Wave | 1 | Artifact | 2 |
training process was performed to prevent errors. The post-training process was created by considering the overlapped epileptic discharge samples. Those points were re-analysed by post-training iterations, and the absolute results were obtained.

After completing the identification of the epileptic discharges, frequency analysis was performed using the Welch method. The mean frequency and mean amplitude of all of the channels of the EEG recordings were calculated. Figure 1 demonstrates the analysis process of the study visually.

All of the EEG analyses in this study were performed on an Ubuntu 20.04.2 LTS Operating System with the MNE Package and the developed software using Python 3.7.6.

Statistical Analysis

Data analyses were performed using IBM SPSS Statistics for Windows 23.0 (IBM Corp., Armonk, NY, USA). Whether the distribution of continuous variables was normal or not was determined using the Kolmogorov-Smirnov test. The Levene test was used for the evaluation of the homogeneity of the variances. Unless specified otherwise, the continuous variables were presented as the mean ± standard deviation (SD) for normally distributed data, and median and range (ie minimum and maximum values) for data with skewed distribution. Categorical variables were given as the number (n) or percentage (%). The student t-test was used to compare the normally distributed continuous variables between 2 independent groups, while the Mann-Whitney U test was implemented for comparing the non-normally distributed data. Categorical variables were compared using the Pearson chi-square test or Fisher exact test. Correlations between the variables were evaluated using the Pearson or Spearman correlation analysis. P < 0.05 was accepted as statistically significant. The 2-tailed testing was applied.

Results

The target population of this study included 40 patients and 40 controls. The primary caregivers of 5 patients did not consent to the EEG and 3 patients and 3 controls with inconclusive EEG data were excluded. Thus, the entire study cohort consisted of 69 patients. Among these patients, 32 were COVID-19-positive, and 37 were assigned to the control group (Figure 2). The COVID-19 patients had either mild (n: 20, 62.5%) or moderate disease (n: 12, 37.5%) based on the referred classification (22). Of the patients, 2 reported a loss of taste and smell, while 4 patients reported intermittent headaches, which started during their COVID-19 infection. None of the enrolled patients had a history of epilepsy.
The EEGs were performed for the patient group at an average of $4.8 \pm 0.6$ months after they had become infected with COVID-19. Eight of 32 (25%) COVID-19 patients and 2 of 37 (5.4%) controls showed interictal epileptiform discharges, meaning spikes, polyspikes, sharp waves, or spike and slow-wave complexes without observed clinical seizures.

In the COVID-19-positive children, the sharp slow-waves, spikes, spike slow-wave amplitudes, and spikes and spike slow-wave median amplitudes were higher than those of the control group in a statistically significant manner. In the pooled analysis, the spikes and spike slow-wave amplitudes were also statistically significant higher, at $P=0.008$. The global mean frequency, sharp slow wave, and spike slow-wave indices were also significantly higher when compared to the control group (Table 2).

The COVID-19-positive patients and the control group were compared with regard to the amplitude and frequency from each electrode. Additionally, both intragroup and intergroup comparisons were performed using the data obtained from the bilateral hemispheric electrodes (Tables 3 and 4).

The average frequency values obtained from the Fp2, F3, F4, F7, F8, and Fz electrodes in the COVID-19-positive patients were significantly lower when compared to the healthy controls. The intragroup comparisons of the average frequency values obtained from the right and left frontal lobes were similar (Table 3). There was no statistically significant difference concerning the average amplitude values obtained from the frontal electrodes between the groups. Statistically significant lower average frequency values were obtained from all of the central electrodes in the COVID-19-positive patient group when compared to the control group. The intragroup comparisons in both of the groups revealed similar frequency values when the right and left central lobe electrodes were compared. Although the average frequency values obtained from all of the temporal electrodes were lower in the COVID-19 patients when compared to the control group, a statistically significant difference was only found between the T4 and T6 values. Moreover, in the COVID-19-positive patient group, the average frequency values were lower in T4 than in T3 and in T5 than in T6, in a statistically significant manner. The average frequency values obtained from the P4 and Pz electrodes were significantly lower in the COVID-19 patient group when compared to the control group. The COVID-19 group had significantly higher average frequency values in the left occipital electrodes when compared to the right occipital electrodes (Table 3).

The average amplitudes obtained from the Fp2 electrode were significantly lower when compared to the Fp1 electrode in the control group. In the COVID-19 group, the average amplitudes obtained from the Fp2 electrode were lower than those from the Fp1 electrode, those from the F4 electrode were lower than those from the F3 electrode, and those from the electrode were lower than those from the F7 electrode, in a statistically significant manner. The average amplitude

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Figure 2. The flowchart of the study.
Table 2. Comparison of demographic and electrographic data between COVID-19 positive patients and the control group.

|                  | Control Group (n:37) | COVID-19 positive group (n:32) | p     |
|------------------|----------------------|--------------------------------|-------|
| Age              | 15 (7–17)            | 14.5 (6–17)                    | 0.192 |
| Gender, male     | 10 (27%)             | 11 (34.4%)                     | 0.508 |
| Sharp slow-wave  | 2 (0–5)              | 3 (0–14)                       | 0.022 |
| amplitude       |                      |                                |       |
| Sharp wave amplitude | 20.0 ± 15.1         | 15.5 ± 12.5                    | 0.183 |
| Sharp and sharp slow-wave amplitudes | 11.14 ± 7.83 | 9.84 ± 5.76 | 0.444 |
| Spike wave amplitude | 2 (0–6)            | 3 (0–13)                       | 0.008 |
| Spike slow-wave amplitude | 4 (0–7)            | 4.5 (0–13)                     | 0.030 |
| Spike and spike slow-wave amplitudes | 3 (0–5.5)   | 3.5 (0.5–11)                   | 0.008 |
| Global mean amplitude | 25.1 (9.3–146.2)    | 29.4 (11.4–159.2)              | 0.248 |
| Global mean frequency | 24.2 (5.6–56.2)      | 11.8 (2.9–46.7)                | 0.004 |
| Sharp slow index | 0.003 (0–0.008)      | 0.005 (0–0.023)                | 0.022 |
| Spike slow index | 0.007 (0–0.012)      | 0.008 (0–0.022)                | 0.030 |

Continuous variables are expressed as either the mean ± standard deviation (SD) or the median (minimum value-maximum value), and categorical variables are expressed as either frequency or percentage. Continuous variables were compared with the Student t-test or the Mann Whitney u test and categorical variables were compared using Pearson's chi-square test or Fisher exact test.

values obtained from the central, parietal, and occipital electrodes were statistically similar in the intragroup, intergroup, and interhemispheric comparisons. When the average amplitude values were considered, even though all of the amplitude values obtained from the temporal electrodes of COVID-19 patients were higher than in the control group, the only statistically significant difference was observed in the T5 electrode values. While the intragroup values of the control group were similar, the COVID-19 patient group had lower average amplitude values; the T3 and T5 values were lower than the T4 and T6 values, which meant that the left hemisphere had higher average amplitude values than the right hemisphere (Table 4).

No statistically significant difference was detected in the amplitudes of the spike-waves, spikes and slow waves, and sharp slow waves, spike slow wave index, sharp slow wave index, and global and local frequency and amplitudes among the mildly (n: 20) and moderately (n:12) infected patients.

Discussion

Age- and sex-matched groups of 32 COVID-19 infected patients and 37 control group participants were included in the current study in order to evaluate whether there was a significant difference between the electrophysiological patterns on their EEG records. The EEG records were recorded at 4.8 ± 0.6 months after the patients had presented a nasopharyngeal real-time PCR-positive results. The majority of the currently evaluated EEG reports demonstrated generalized slowing, focal slowing, epileptiform discharges with seizures, and status epilepticus for the COVID-19 patients. Within the present study, the amplitude of sharp slow waves, spike-waves, and spike slow waves were found to be higher in the children who had a previous COVID-19 infection in a statistically significant manner, even though there was no previous history of seizures during the course of COVID-19 infection. In addition, spike-wave index and sharp slow wave indices were significantly higher in the COVID-19-positive patient group. The rate of epileptic discharges were 25% within COVID-19 infected group. In addition, epileptic discharges were detected in the control group as well as in the COVID-19 patients. Epileptiform discharges can be seen in healthy children with no clinical symptoms and such cases require no antiepileptic treatment. Okubo et al reported the observation of epileptiform discharges in healthy children at a rate of 5%. Similarly, the rate of epileptiform discharges were 5.4% in control group. In a recent study of 183 hospitalized children with suspected encephalitis, 22 (12%) had coronavirus infection (type undetermined) that was detected via anti-CoV-IgM, and among them, 5 of these 22 (23%) had seizures. In another study evaluating the neurological manifestation of COVID-19 patients, the rate of seizures was documented as 0.5%. EEG abnormalities were documented to be common in a review of 617 COVID-19-positive patients, which included EEG scores from 84 studies. Intermittent discharges were observed within that study.36 Epileptic activity was reported at a rate of 19.2% in a review of 177 patients. In another cohort of 110 patients, among 24 patients who had seizures, 21 had no prior history of epilepsy. In the present study, epileptic discharges were observed with increased indices of the spike-wave and sharp slow waves in infected children without clinical seizures. Electrographic seizures were also reported in recent studies of COVID-19-infected patients that support the findings of the present study. However, those studies mostly involved symptomatic cases. In contrast, no electrographic seizures were reported in case series evaluating 22, 36, 10 patients who underwent EEG monitoring. This emphasizes the importance of other mechanisms for seizure development rather than hypoxia, shock, or complications of severe infection.

The global mean frequency was shown to be lower and the global mean amplitudes were significantly higher in the COVID-19-infected group. Higher amplitudes, in addition to decreased frequency, are especially seen in increased synchronization of the neurons, which is a finding for dysfunction, apart from the etiological factor. It is obviously seen as rhythmic delta activity in cases related to multiple aetiologies, such as metabolic, toxic, or various diffuse or focal intracranial pathologies with no specificity. In an EEG study evaluating 40
Table 3. Intergroup and intragroup comparisons of frequency values obtained from all electrodes.

|                        | Control Group (n:37) | COVID-19 positive group (n:32) | Independent groups P value |
|------------------------|----------------------|-------------------------------|----------------------------|
| **Frequencies recorded from frontal and frontopolar electrodes** |                      |                               |                            |
| Fp1                    | 20.5 (3.6–50.4)      | 9.3 (3.5–48.6)                | 0.067                      |
| Fp2                    | 17.8 (5.2–55.2)      | 9.9 (2.5–57.4)                | 0.012                      |
| Dependent groups P value | 0.999                | 0.421                         |                            |
| F3                     | 12.4 (4.9–56.5)      | 7.8 (2.9–48.4)                | 0.002                      |
| F4                     | 19.9 (5.3–55.9)      | 7.6 (2.9–52.3)                | 0.006                      |
| Dependent groups P value | 0.645                | 0.155                         |                            |
| F7                     | 21.4 (3.6–53.2)      | 8.2 (2.7–44.5)                | 0.003                      |
| F8                     | 20.5 (5.1–56.6)      | 7.1 (2.9–50.2)                | 0.001                      |
| Dependent groups P value | 0.464                | 0.681                         |                            |
| Fz                     | 25.3 (7.2–57.9)      | 9.3 (2.6–51.0)                | 0.002                      |
| Fpz                   | 10.5 (4.3–53.3)      | 7.9 (2.6–43.4)                | 0.062                      |
| **Frequencies recorded from central electrodes** |                      |                               |                            |
| C3                     | 22.5 (6.3–56.7)      | 12.6 (2.6–47.7)               | 0.005                      |
| C4                     | 22.5 (6.5–56.3)      | 9.9 (2.6–49.3)                | 0.007                      |
| Dependent groups P value | 0.346                | 0.411                         |                            |
| Cz                     | 24.2 (5.6–56.2)      | 11.8 (2.9–46.7)               | 0.006                      |
| **Frequencies recorded from temporal electrodes** |                      |                               |                            |
| T3                     | 18.5 (5.6–56.5)      | 13.7 (2.4–46.93)              | 0.071                      |
| T4                     | 18.5 (6.5–57.1)      | 6.9 (2.5–48.6)                | 0.003                      |
| Dependent groups P value | 0.521                | 0.043                         |                            |
| T5                     | 10.8 (4.1–53.6)      | 7.8 (2.5–49.8)                | 0.073                      |
| T6                     | 15.5 (4.5–56.3)      | 8.3 (2.5–44.2)                | 0.002                      |
| Dependent groups P value | 0.446                | 0.032                         |                            |
| **Frequencies recorded from parietal electrodes** |                      |                               |                            |
| P3                     | 21.7 (5.5–50.5)      | 16.4 (2.4–48.5)               | 0.075                      |
| P4                     | 27.1 (7.0–56.2)      | 16.8 (2.4–54.7)               | 0.005                      |
| Dependent groups P value | **0.010**            | 0.681                         |                            |
| Pz                     | 31.5 (6.2–56.5)      | 20.8 (2.6–51.4)               | 0.006                      |
| **Frequencies recorded from occipital electrodes** |                      |                               |                            |
| O1                     | 15.6 (4.1–53.4)      | 8.1 (2.4–50.1)                | 0.040                      |
| O2                     | 18.1 (3.4–54.5)      | 7.5 (2.4–46)                  | 0.001                      |
| Dependent groups P value | 0.541                | 0.014                         |                            |
| Oz                     | 12.3 (4.2–56.8)      | 6.7 (2.6–45)                  | 0.007                      |

Non-normally distributed continuous variables are expressed as either the median (minimum value-maximum value). Statistical analysis differences in not normally distributed variables between two independent groups were compared by Mann Whitney U test, and not normally distributed variables between two dependent groups were compared by Wilcoxon test.

EEGs from 36 COVID-19 patient generalized periodic discharges, multifocal periodic discharges or rhythmic delta activity was reported in 13 (32.5%) of the records. However, there were major differences with the current study, as they involved symptomatic adult patients with multiple comorbidities. Diffuse theta and delta slowing was also reported in another study that evaluated 20 EEG records from COVID-19 patients with altered mental status. In a study that included 15 adult patients who had a COVID-19 infection with suspected encephalopathy, the EEG results revealed slowing of the background activity, ranging from 4 to 8 Hz (with theta prevalence in 5 cases and intrusions of theta/delta activity in 4 cases), and focal delta of the theta waves predominantly over the frontal or central regions (3 patients). Likewise frontal and central slowing with significantly decreased frequencies were documented in this study. The frequencies of the frontal areas recorded by the Fp2, F3, F4, F7, F8 electrodes were significantly lower when compared to the control group. Moreover, the amplitudes of the left temporal areas (Fp1, F3, and F7) significantly increased, and demonstrating bifrontal involvement with left predominancy. This significant decrease in the frequency was also recorded in central areas. For the temporal lobes, the frequency of the T4 and T6 electrodes was diminished and this decrease was also obvious among 2 hemispheres of the COVID-19 patients. In a study supporting these findings, mostly the frontal area was affected, including local background slowing, intermittent discharges, and rhythmic delta activity. The authors also reported that the EEG abnormalities
correlated with disease severity and pre-existing neurological conditions like epilepsy. Generalized EEG slowing was shown in 16 of 18 (88.9%) COVID-19-positive patients with anterior (bifrontal) prevalence of the slow waves found in 10 of 18 (55.6%) COVID-19-positive patients. In an additional study conducted by Cecchetti et al., the severity of COVID-19 disease was correlated with the degree of EEG alteration. In the current study, CNS dysfunction was observed without pre-existing neurological conditions or clinical involvement of the CNS. Not only fronto-central areas, but also P4, 01, and O2 had significantly lower frequencies in the COVID-19-positive patient group. Parieto-occipital involvement was significant for a small group of electrodes. Parieto-occipital involvement was documented in a study of neuroimaging. In that study, a cortical FLAIR signal abnormality was reported in 10 of 27 (37%) patients with COVID-19 infection who were admitted to the intensive care unit. Among the 27 patients, frontal, parietal, occipital, and temporal signal abnormalities were detected in 4, 3, 4, and 1 patients, respectively. No reports were documented regarding neurological involvement by means of electroneurophysiology or neuroimaging in patients with asymptomatic or mildly symptomatic COVID-19 infection.

### Table 4. Intrigroup and intergroup comparisons of amplitude values obtained from all electrodes.

| Electrode Location                  | Control Group (n:37) | COVID-19 positive group (n:32) | Independent groups P value |
|-------------------------------------|----------------------|-------------------------------|---------------------------|
| Amplitude recorded from frontal and frontopolar electrodes |                      |                               |                           |
| Fp1                                 | 12.9 (5.3–62.7)      | 14.7 (4.5–59)                 | 0.847                     |
| Fp2                                 | 10.4 (1.5–72.7)      | 5.6 (1.5–46.3)                | 0.067                     |
| **Dependent groups P-value**        | **0.014**            | <0.001                        |                           |
| F3                                  | 12.7 (6.0–69.0)      | 19.0 (6.3–47.9)               | 0.189                     |
| F4                                  | 13.2 (6.2–77.1)      | 14.9 (4.7–61.8)               | 0.589                     |
| **Dependent groups P-value**        | **0.338**            | **0.035**                     |                           |
| F7                                  | 16.5 (6.8–74.9)      | 17.3 (7.9–92.3)               | 0.782                     |
| F8                                  | 16.2 (6.5–117.9)     | 12.9 (6.1–45.3)               | 0.363                     |
| **Dependent groups P-value**        | **0.405**            | **0.003**                     |                           |
| Fz                                  | 19.9 (6.1–61.2)      | 16.4 (3.7–90.4)               | 0.697                     |
| Fpz                                 | 13.7 (7.5–69.5)      | 17.9 (7.2–40.4)               | 0.201                     |
| Amplitude recorded from central electrodes |                      |                               |                           |
| C3                                  | 23.5 (9.6–66.7)      | 26.3 (7.9–85.2)               | 0.376                     |
| C4                                  | 23.8 (8.9–97.2)      | 26.6 (7.3–69.7)               | 0.547                     |
| **Dependent groups P-value**        | **0.566**            | 0.155                         |                           |
| Cz                                  | 23.2 (9.3–74.4)      | 27.4 (11.4–82.4)              | 0.115                     |
| Amplitude recorded from temporal electrodes |                      |                               |                           |
| T3                                  | 19.2 (9.9–75.9)      | 24 (11.2–52.3)                | 0.229                     |
| T4                                  | 19 (8.4–109.4)       | 19.30 (9–49.1)                | 0.768                     |
| **Dependent groups P-value**        | **0.987**            | <0.001                        |                           |
| T6                                  | 17.8 (10.3–75.9)     | 22.7 (10.4–72.3)              | 0.016                     |
| **Dependent groups P-value**        | **16.9 (8.8–80.7)**  | **17.6 (8.3–44.4)**           | 0.614                     |
| Amplitude recorded from parietal electrodes |                      |                               |                           |
| P3                                  | 22.8 (9.7–78)        | 30.5 (11.5–81.7)              | 0.093                     |
| P4                                  | 25.3 (10.9–94.9)     | 27.0 (10.3–80.1)              | 0.680                     |
| **Dependent groups P-value**        | **0.125**            | 0.688                         |                           |
| Pz                                  | 32.9 (10.6–96.1)     | 32.7 (14.4–72.9)              | 0.944                     |
| Amplitude recorded from occipital electrodes |                      |                               |                           |
| O1                                  | 20.1 (9.7–57.4)      | 22.2 (11.9–71.9)              | 0.410                     |
| O2                                  | 21.2 (8.7–58.1)      | 20.8 (13.9–52.7)              | 0.754                     |
| **Dependent groups P-value**        | **0.635**            | 0.822                         |                           |
| Oz                                  | 16.3 (8–59.5)        | 17.6 (8.5–41.3)               | 0.555                     |

Non-normally distributed continuous variables are expressed as either the median (minimum value-maximum value). Statistical analysis differences in not normally distributed variables between two independent groups were compared by Mann Whitney U test, and not normally distributed variables between two dependent groups were compared by Wilcoxon test.
Among patients with COVID-19, the amplitudes of the left frontal and left temporal were significantly higher when compared to the right. This may have been due to a higher involvement of those areas, in addition to background slowing.

No statistically significant difference was detected for the amplitudes of the spike-waves, spikes and slow-waves, and sharp slow waves, spike slow-wave index, sharp slow wave index, and global and local frequency and amplitudes among the mildly (n: 20) and moderately (n: 12) infected patients. In a review synthesizing the data of EEG scores in COVID-19-related encephalopathy, the EEG abnormalities were determined to be correlated with disease severity. The lack of a significant difference among the mild and moderate patient groups in that study may have been caused by the small sample size or mild to moderate course of the infection.

The COVID-19-positive children, who presented with mild to moderate symptoms, also presented with slowing down background activity, which was detected based on the frequency of the basal rhythm using an EEG analysis and the presence of epileptiform discharges. These effects were observed 4–6 months after the recovery of COVID-19 infection. This may have been related to the post-infectious stimulation of the immune system and ongoing immunological processes. The long-term effects of COVID-19 infections on the CNS are currently poorly defined among all age groups, and especially in children, which warrants further studies.

As for the limitations of the present study, there were no prior EEG records for the COVID-19-infected children, as they were healthy children without neurological problems prior to infection, no psychological tests had been performed clinically, and there was a lack of the presence of identical studies involving children to compare the results with. Additionally, the study had a relatively low sample size and, there was no correction for multiple testing in statistical analysis, the results have to be interpreted with caution for this reason.

**Conclusion**

Electrophysiological dysfunction of the CNS was observed in COVID-19-positive children in the current study. A near-global involvement of background activity with decreased frequency, in addition to epileptic discharges, were recorded in mild to moderately COVID-19 infected children post-recovery. Further studies with an increased sample size and long-term medical follow-ups are essential to demonstrate whether those changes were transient or will result in a permanent dysfunction.

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**Author Roles**

All of the authors (AY, ÖYK, BS, BŞ) contributed to the design of the study, contributed to the analysis of the data, drafting of the manuscript and, critically revising the manuscript for important intellectual content. All of the authors gave the final approval, and agreed to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

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**Ethical Approval**

This study was approved by the Ethical Review Committee of Ankara Research and Training Hospital (Ethical approval number: 549).

**Author Contributions**

All authors were involved in developing, editing, writing and revising the paper. All authors satisfy the ICMJE criteria for authorship.

**Declaration of Conflicting Interests**

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