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Subacute neurological sequelae in mild COVID-19 outpatients

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ABSTRACT

Subacute neurological sequelae in mild COVID-19 outpatients

Introduction: Neurological aspect of COVID-19 is less understood compared to its respiratory and systemic effects. We aimed to define subacute neurological sequelae in patients who recovered from mild COVID-19.

Materials and Methods: This study enrolled long COVID patients who had mild infection, were non-hospitalized, and admitted to our hospital with neurological complaints occurring after COVID-19. The evaluation included detailed history of the symptoms, neurological examination, blood tests and necessary investigations relevant to their personal medical situation, and also a retrospective inquiry about their respiratory and neurological status during the acute phase of infection. Descriptive statistical measures, Chi-square and Student's t-test were utilized.

Results: We identified 50 patients (29F/21M) with a mean age of 36.9 ± 1.6 (mean ± SEM). The average time from COVID-19 to admission was 99 days (min-max= 15-247). Most frequent neurological complaints were headache (42%) and cognitive dysfunction (42%). Sleep disturbance (36%), prolonged anosmia (30%), prolonged ageusia (22%), fatigue (22%), and dizziness (8%) followed. Most patients with headache experienced headache also as an acute manifestation of COVID-19 ($p=0.02$). Acute-stage sleep disorders were found to be more associated with subacute cognitive symptoms than other central symptoms ($p=0.008$). The most common neurological symptom in the acute phase was headache (74%). Six patients, despite the absence of any

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acute-stage neurological symptoms, presented with emergence of subacute neurological sequela. There were only five patients with pulmonary involvement during the acute stage, who were not different from the rest of the cohort in terms of neurological sequelae. There was no increase of inflammatory markers in the blood tests at the subacute stage, or no association of the symptoms to biochemical parameters.

Conclusion: This study gives a description of neurological sequelae of mild COVID-19 at the subacute stage, in a relatively young group, and reveals that cognitive disturbances, as well as headache, are quite frequent.

Key words: Neuro-covid; headache; cognitive disturbance; inflammation; long covid

ÖZ

Ayaktan hafif COVID-19 hastalarında subakut nörolojik sekeller

Giriş: COVID-19'un nörolojik yönü, solunumsal ve sistemik etkilerine kıyasla daha az bilinmektedir. Bu çalışmada, hafif COVID-19 geçirmiş hastalarda subakut nörolojik sekelleri tanımlamayı amaçladık.

Materyal ve Metod: Çalışmaya hafif COVID-19 geçirmiş, hastaneye yatırılmadan izlenmiş ve sonrasında nörolojik şikayetlerle bize başvuran uzun COVID hastaları alındı. Değerlendirme sırasında semptomların ayrıntılı anamnezi alındı, nörolojik muayene yapıldı; kan testleri ve kendi tıbbi durumlarıyla ilgili gereken araştırmalar, ayrıca enfeksiyonun akut fazı sırasında respiratuvar ve nörolojik durumlarına yönelik geriye dönük bir sorgulama yapıldı. Tanımlayıcı istatistiksel parametreler, Ki-kare ve Student t-testi kullanıldı.

Bulgular: Ortalama yaşı 36.9 ± 1.6 (ortalama $\pm$ SH) olan 50 hasta (29K/21E) tespit edildi. COVID-19'dan kabule kadar geçen ortalama süre 99 gündü (min-maks= 15-247). En sık görülen nörolojik şikayetler baş ağrısı (%42) ve bilişsel işlev bozukluğu (%42) idi. Bunu uyku bozukluğu (%36), uzamış anozmi (%30), uzamış aguzi (%22), yorgunluk (%22) ve baş dönmesi (%8) izlemekteydi. Baş ağrısı olan hastaların çoğu, aynı zamanda COVID-19'un akut bir belirtisi olarak da baş ağrısını yaşamışlardı ($p= 0.02$). Diğer merkezi semptomlara göre akut dönemdeki uyku bozukluklarının subakut kognitif semptomlarla daha fazla ilişkili olduğu bulundu ($p= 0.008$). Akut dönemde en sık görülen nörolojik semptom baş ağrısıydı (%74). Altı hasta herhangi bir akut dönem nörolojik semptomu olmamasına rağmen subakut nörolojik sorun gelişimi ile baş vurmuştu. Akut dönemde pulmoner tutulumu olan sadece beş hasta vardı ve nörolojik sekeller açısından kohortun geri kalanından farklılık göstermiyordu. Subakut aşamada kan testlerinde enflamatuvar belirteçlerde artış yoktu ve semptomların biyokimyasal parametrelerle ilişkisi tespit edilmedi.

Sonuç: Bu çalışma, nispeten genç bir grupta subakut aşamada hafif COVID-19'un nörolojik sekellerinin bir tanımını vermekte ve baş ağrısının yanı sıra bilişsel bozuklukların oldukça sık olduğunu ortaya koymaktadır.

Anahtar kelimeler: Nöro-covid; baş ağrısı; kognitif bozukluk; enflamasyon; uzun covid

INTRODUCTION

As of July 31 2021, the COVID-19 outbreak has infected more than 198 million people worldwide and caused more than 4.2 million deaths (<https://worldometers.info/coronavirus/>). It is known since the first reports from China where the pandemic started that the disease can affect the nervous system (1). Neurological symptoms such as anosmia, ageusia, nausea, dizziness, headache, and myalgia are frequently reported by the patients during SARS-CoV-2 infection (2,3). More severe neurological complications may also develop due to SARS-CoV-2 infection, like meningoencephalitis, stroke and other cerebrovascular diseases, Guillain-Barre syndrome (GBS), intracranial hypertension, myelitis, and encephalopathy (4).

Several mechanisms have been proposed for these SARS-CoV-2 associated neurological complications, some of which are direct neuroinvasion, neuroinflammation, autoimmunity, cytokinemia, endothelitis or other vascular causes (5-8). However, neuro-pathogenesis is not straightforward, yet.

Information on the neurological involvement of COVID-19 in the literature mostly comes from case reports, case series and meta-analyses. The prevalence of neuro-COVID, risk factors or predictive information for the development of neurological involvement are not known clearly. Recent larger studies on neurological involvement are based on groups of hospitalized patients (9-14). Some are reports of acute complications (stroke, venous thrombosis, encephalopathy, GBS etc.) in relatively serious COVID-19 patients (15-17). Therefore, the neurological aspect of this disease on the broad-spectrum is less known compared to its respiratory and other systemic effects.

Recently, mental disorders referred to as "brain fog", have been mentioned in individuals who have had COVID-19 and survived the disease (18,19). Ongoing neuro-psychological symptoms along with cardiac and respiratory complaints have been included under the term 'long COVID' (20-22). These abnormalities are considered to be caused by continuing inflammation resulting from COVID-19, however, it is not yet

known to which clinical and biochemical features these cognitive abnormalities are related.

In this study, we aimed to examine long COVID patients presenting with neurological symptoms after acute illness in outpatient clinics, and to define sub-acute neurological sequelae in a cohort of mild COVID-19 patients. Our hospital is a tertiary private university hospital, and did not serve as an active pandemic center for hospitalization. Hence, most of the admissions are mild COVID-19 cases, and the data obtained reflect the neurological profile of a more homogeneous COVID spectrum. In this regard, we think that it will make an important contribution to the literature.

MATERIALS and METHODS

Patient Group

This study includes a cohort of non-hospitalized patients who had COVID-19, recovered, and admitted to our hospital with the neurological complaints occurring after COVID-19.

Inclusion criteria were: 1. having SARS-CoV2 PCR (+) test result in the acute stage 2. aged between 18-80 years 3. having neurological symptoms that persisted after COVID-19 or 4. having neurological complaints that started after COVID-19.

Exclusion criteria were: 1. having neurological symptoms before COVID-19 and reporting no change in the symptoms after this infection (unrelated and unaffected neurological complaints) 2. having severe COVID-19 that necessitated hospitalization.

Neurological Evaluation and Pulmonary Assessment

We included all the patients that met the inclusion criteria, consecutively in our outpatient clinics. Patients underwent routine neurological examination and necessary biochemical investigations relevant to their personal medical situation. The evaluation included detailed anamnesis about frequent neurological complaints seen after COVID-19 (headache, characteristics of headache, smell and taste problems, cognitive complaints, sleep disturbance, fatigue, myalgia). All the patients were also inquired retrospectively about their respiratory, metabolic and neurological status during the acute phase of COVID-19 infection and infection severity was confirmed by two pulmonologists (23). Radiological investigations and medical notes belonging to the acute stage were checked from the health records and pneumonia

cases were identified. All were examined for disc edema by ophthalmologists. The inquiry included the following symptoms:

Acute stage:

- Headache
- Disturbance in smell
- Disturbance in taste
- Confusion
- Fever, cough, sputum, back pain
- Tingling in the hands, feet, other parts of the body
- Dizziness
- Nausea
- Sleep disturbances
- Symptoms related to other systems

Statistical Analysis

Descriptive statistical measures were used to define the frequencies of each neurological symptom. The analysis of categorical variables was done by chi-square test. The comparisons of biochemical parameters were done by two-tailed student's t-test after normal distribution was confirmed. Type I error probability was accepted as $\alpha = 0.05$. Exact p values were reported.

Data Availability

The data are not publicly available due to ethical considerations. Information can be accessed upon reasonable request from the corresponding author.

RESULTS

We identified 50 patients admitted to our hospital with neurological complaints after COVID-19 (Table 1). Mean age of the patients was 36.9 ± 1.6 (mean $\pm$ standard error of mean, SEM) (min-max= 18-70; median= 36). Twenty-nine of the patients were females (mean age 36.0 ± 2.2) and 21 were males (mean age 38.1 ± 2.5). The average time from COVID-19 disease to admission was 99 days (min-max: 15-247; median=104). Only five of them had pneumonia during the acute illness, all of which were mild and treated at home.

Neurological examination of our cohort revealed no abnormal signs or focal findings, apart from decreased

Table 1. General and laboratory features of the study cohort (n= 50)

Age, years (mean±SEM)	36.9 ± 1.6	
Sex (F/M)	29/21	
Education, years (mean±SEM)	14.3 ± 0.2	
Days from COVID-19 to admission, median (min-max)	104 (15-247)	
Treated by favipravir (no of patients)	49	
Pneumonia	N= 5	
Hemoglobin, g/dL (mean±SEM)	13.9 ± 0.2	
Leukocyte, per mm ³ (mean±SEM)	6705 ± 256	
CRP, mg/L (mean±SEM)	2.7 ± 0.6	Reference: 0-5
Ferritin, ng/mL (mean±SEM)	89.7 ± 19.7	Reference: 15-150
Neutrophil/lymphocyte ratio, (mean±SEM)	1.6 ± 0.07	
Vitamin D3, ng/mL (mean±SEM)	20.9 ± 2.7	Reference: 25-80
Vitamin B12, pg/mL (mean±SEM)	447.2 ± 42.9	Reference: 197-866

SEM: Standard error of mean; min: Minimum; max: Maximum; CRP:C-reactive protein.

Laboratory tests belong to the subacute period of infection, which is the time of admission.

olfactory and gustatory sensation in some patients. All patients were examined by ophthalmologists. No optic disc edema or retinal pathology was found in any of them. C-reactive protein (CRP) and ferritin levels were in normal range for all of the patients. Mean blood neutrophil/lymphocyte ratio of the cohort, which is accepted as an inflammatory mark-

er, was 1.6 ± 0.07 (mean ± SEM) and mean vitamin D level was low in the study population (20.9 ± 2.7 ng/mL, mean ± SEM).

The frequency of neurological complaints expressed by the patients is shown in Figure 1.

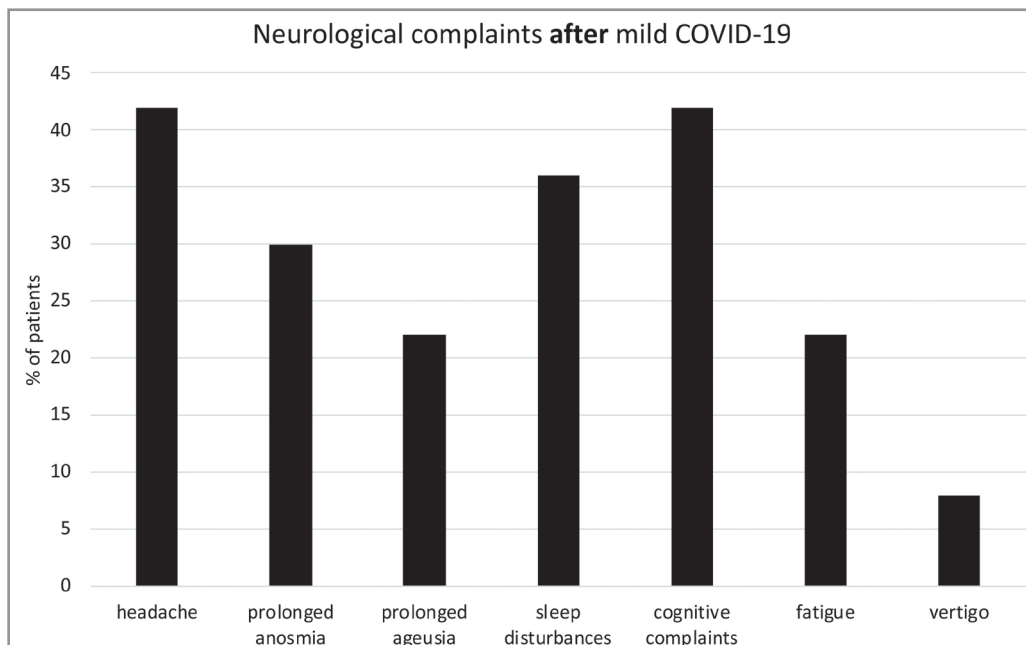


Figure 1. The distribution of neurological complaints among the outpatients who had recovered from mild COVID-19 (subacute period).

Headache

Forty two percent of the patients (n= 21) complained of headache. This pain was defined as either “headache after having COVID-19, that is new-onset and different from the previous ones”, or “headache with increased frequency or intensity after COVID-19”. Four of these patients were previously known to have migraine. Four other patients had no previous migraine attacks, but their pain characteristics were suggestive of migraine (unilateral, throbbing and severe headache). One patient started to experience a type of headache matching the characteristics of tension type headache.

One of the patients with migraine presented with a severe and persistent migraine attack two weeks after COVID infection. This patient, who was diagnosed with status migranosus in the follow-up, was treated with intravenous (IV) dexamethasone since no stable

response was obtained from parenteral non-steroidal anti-inflammatory drugs (NSAIDs) and valproic acid treatments. Corticosteroids terminated her headache.

There was no difference between men and women in terms of suffering from headache (Chi-square test, $p=0.63$). Vitamin B12 or Vitamin D levels were not different in headache sufferers compared to the ones without headache (in patients with headache VitB12= 502 ± 100 pg/mL, VitD= 23.4 ± 5.1 ng/mL; in patients without headache VitB12= 422 ± 45 pg/ml, VitD= 19.0 ± 2.7 ng/mL, mean $\pm$ SEM; T-test, $p=0.49$ and $p=0.43$ respectively). Neutrophil/lymphocyte ratio appeared to be lower (1.36 ± 0.11 , mean $\pm$ SEM) in the headache group when compared to the ones without headache (1.80 ± 0.11 , mean $\pm$ SEM). This difference was statistically significant (T-test, $p=0.01$); however, clinical importance is vague (Figure 2).

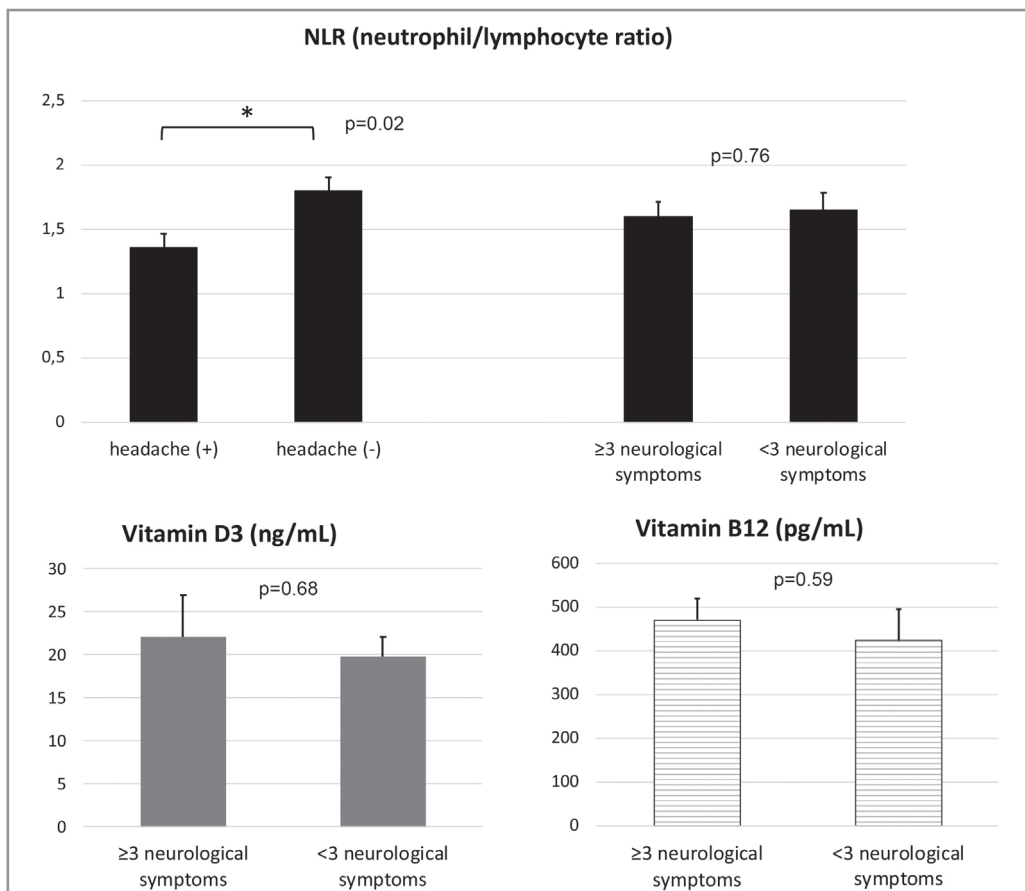


Figure 2. Neutrophil/lymphocyte ratio (NLR), Vitamin D and B12 levels did not differ significantly in the patients who had more neurological symptoms. NLR was shown to be mildly (but significantly) lower in the patients who suffered headache in the subacute period.

* $p=0.02$



A substantial portion of these patients (90%) experienced headache also as an acute manifestation of the SARS-CoV-2 infection, and this difference in distribution was significant (Chi-square test, $p = 0.02$).

Cognitive Complaints

Cognitive problems emerged as a neurological complaint that were as common as headache in our patients. Forty-two percent of the patients ($n = 21$) suffered from mild-to-moderate cognitive strain in daily life. It was often expressed as attentional and focusing problems, sometimes as an increasing 'forgetfulness' (having to re-read the sentences that you have just read, messing up the order while knitting, forgetting the things you got up to do and coming back without doing them, distraction while talking and forgetting the beginning of the conversation, etc.). One patient complained of difficulty in finding words and hesitancy in speaking. No lesion was detected in the brain magnetic resonance imaging (MRI) of this patient.

Only one of these cases presenting with cognitive complaints experienced no neurological symptoms in the acute period. Fifteen of them had experienced three or more neurological symptoms in the acute infection. Among the neurological symptoms encountered during COVID-19 (in the acute period), sleep disorders were found to be more associated with subacute cognitive symptoms than other central symptoms (headache, dizziness, nausea, confusion, fatigue, anosmia, ageusia) (Chi-square test, $p = 0.008$). The rate of persistent (subacute) sleep disturbance in patients with cognitive complaints was 48% ($n = 10$) and did not show a significant difference compared to those without ($p = 0.16$). None of the vitamin B12, vitamin D levels or neutrophil/lymphocyte ratio (NLR) showed a significant difference compared to the subjects without cognitive symptoms (in patients with cognitive complaints $\text{VitB12} = 475 \pm 64 \text{ pg/mL}$, $\text{VitD} = 24.5 \pm 4.4 \text{ ng/mL}$; in patients without cognitive complaints $\text{VitB12} = 411 \pm 55 \text{ pg/mL}$, $\text{VitD} = 17.5 \pm 2.8 \text{ ng/mL}$, mean $\pm$ SEM; t-test, $p = 0.46$ and $p = 0.20$, respectively).

Anosmia and Ageusia

Thirty percent of the patients complained of prolonged anosmia. The mean duration of anosmia was calculated as 49 days for this cohort (min-max= 7-150 days). Prolonged ageusia was present in 22% of the patients. The average duration was 42 days

(4-150 days). The patients in this group stated that the improvement in both senses was slow and partial.

Sleep Disorders

The frequency of sleep disturbances in the subacute period in patients with mild COVID-19 was 36% ($n = 18$). It was noted that both excessive sleepiness and insomnia could be seen. Only 6 of these patients stated that they had sleep problems during the acute infection period ($p = 0.79$). When the patients with sleep problems were examined one by one, it was noticed that four of the patients had intense anxiety symptoms.

Fatigue

Eleven patients (22%) suffered from ongoing fatigue after COVID-19. Four of them had significantly low levels of vitamin D and were treated accordingly. Other four patients had appeared to have hematological abnormalities at the acute phase and three of them also had elevated acute phase reactants during COVID-19. One of those latter patients also had a chronic inflammatory spondyloarthropathy. None of these subjects was in a dysthyroid state.

Neurological Symptoms in the Acute Stage

All of the patients were quarantined and treated at home due to COVID-19 and none were hospitalized. It was learned that none of our patients experienced severe neurological complications (stroke, meningo-encephalitis, myelitis, Guillain-Barré syndrome, etc.) in the acute period. All but one patient used anti-viral therapy (favipravir) distributed by the state. Only one female patient reported that she did not take the medication because of breastfeeding.

When inquired retrospectively about the infection period, it was understood that 44 out of 50 patients experienced at least one neurological symptom in the acute period. Six patients did not have any neurological complaints in the acute period, but these subjects presented with complaints of dizziness, sleep disturbance, fatigue in the subacute period, and one patient with headache and cognitive problems. The most common neurological symptom in the acute phase was headache, with a frequency of 74% in this cohort. In some patients, headache emerged as the first presentation sign of COVID-19. Anosmia and ageusia were other common neurological symptoms; sleep disturbances, dizziness, paresthesia, nausea and myalgia followed them, respectively

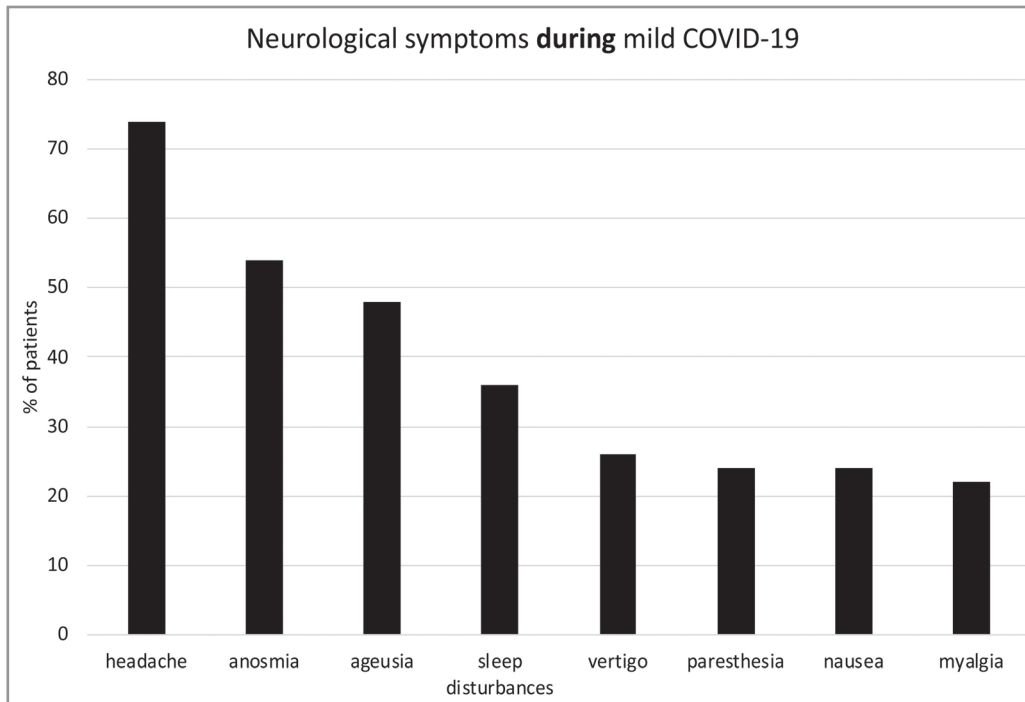


Figure 3. The distribution of neurological symptoms during the acute stage of mild COVID-19 among the outpatients (acute period) (based on inquiry).

(Figure 3). In addition, it was learned that there were confusion and changes in consciousness in three male patients, which coincided with the febrile period and spontaneously resolved in a short time.

We checked whether the patients who had pneumonia exhibited a more severe neurological profile in the subacute period. However, these patients were not different from the rest of the cohort and did not share a common neurological sequela among themselves. Statistical analysis was not performed due to the low incidence of pneumonia cases ($n=5$). We also checked whether the patients who had more neurological symptoms (≥ 3 neurological symptoms) had lower VitB12, VitD levels or had higher NLR. However, the statistical analysis showed no significant difference of these laboratory parameters compared to the patients with less symptoms (Figure 2).

DISCUSSION

The main feature of this study is that it gives a description of neurological sequelae of mild COVID-19 at the subacute (mean 99 days) stage, in a relatively homogenous and young group.

The most frequently reported symptoms were headache and cognitive disturbances.

Headaches occurring during the acute phase of COVID-19 infection are commonly defined as severe, long-lasting and analgesic-resistant (24). During the subacute stage, a considerable number of our patients reported migrainous headaches, including a case of status migrainosus. This raises the possibility that ongoing inflammation that is associated to neurological involvement in COVID-19 might be triggering cortical spreading depression in the brain and might cause migraine-like headaches. Yet, there is no clinical or experimental data in SARS-CoV2 literature to support that idea. Headache of our patients benefited from routine treatment protocols.

Cognitive disturbances were quite frequent in our young cohort (42%, $n=21$). They mostly defined it as an attention/concentration deficit and increased forgetfulness. Fifteen out of 21 patients reported that they had ≥ 3 neurological manifestations during acute COVID-19 period. Among those acute neurological manifestations, sleep disturbances were significantly associated with subacute cognitive abnormalities, acting as a central cue. In other words, a COVID-19 patient who suffered from somnolence or insomnia during the infection was more likely to suffer from cognitive problems after recovery, in our cohort. In a

few studies, executive functions, attention, language and delayed memory have been shown to be affected by COVID-19. However, these evaluations have been performed mostly on hospitalized COVID-19 patients (13,25). In a series of 18 mild-to-moderate COVID-19 patients, the authors have demonstrated sustained subclinical cognitive disturbances by a phone interview after recovery and suggested screening (26). Due to the young age of our cohort, we did not suspect from any neurodegenerative disease with cognitive decline. However, we find it useful to remind that secondary/treatable causes of cognitive dysfunction should not be ignored in COVID-19 patients, as many of our patients had low vitamin D levels.

The frequencies of anosmia and ageusia were 54% and 48% respectively in our patients during the infection phase. These sensory problems are regarded as the initial signs of neuroinvasion by SARS-CoV-2 (27). Research has found an association of anosmia with a milder clinical course (28). Since we did not have a severe COVID-19 group for comparison, our study is far from supporting this finding. Still, it is evident that recovery of these sensations may be as long as five months, and gradual.

We checked whether the patients who had more neurological symptoms (≥ 3 neurological symptoms) had lower VitB12, VitD levels or have higher inflammatory markers. We did not find any association with these biochemical/laboratory parameters. Actually, there was no evidence for an ongoing systemic inflammation in our cohort. Ferritin and CRP levels were in the normal range in all of the patients. During this pandemic, NLR appeared as an inflammatory marker in the acute stage of COVID-19 that correlated with the severity of the disease (29). However, we could not find any increase in the subacute stage in our patients. Immune activation is one of the mechanisms considered as a possible factor underlying the long-lasting neurological symptoms after COVID-19 (3,30). Whether immune dysregulation theory is valid for mild cases, or direct/indirect viral effects in brain tissue are in charge needs to be elucidated. Clues of local inflammation should be sought in cerebrospinal fluid or nervous tissue of patients with neurological sequelae, despite the absence of such markers in mild neurological involvement, yet (11).

Our study was based on a homogenous cohort of long COVID patients who were young-aged, had mild acute infection, and sought medical attention

for their ongoing neurological symptoms. Therefore, the data arising from this study cannot be generalized to the whole population. In many centers around the world, post-COVID-19 clinics are increasingly being implemented to meet the long-term needs of the patients (31). We believe that the findings of this sort of studies will contribute to proper organization of rehabilitative facilities. To unravel the true prevalence and the full-spectrum of the neurological complaints, large-scale community-based clinical trials and registries are needed.

Ethical Committee Approval: This study is approved by TOBB-ETÜ Clinical Researches Ethical Committee (Decision No: 080, Date: 28.04.2021).

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: ATS, EE, KÖ, TM

Analysis/Interpretation: ATS, NN

Data acquisition: ATS, ŞC, EE, BMP, TM, KÖ

Writing: ATS, NN

Clinical Revision: ŞC, BMP, KÖ, TM, EE, NN

Final Approval: All of authors

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