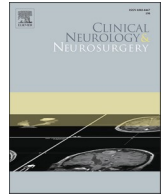




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## The influence of the COVID-19 pandemic on patients with chronic inflammatory demyelinating polyradiculoneuropathy

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### ABSTRACT

**Objectives:** At a time of global health crisis, fear, anxiety, and stress levels increase. The effects of protracted social isolation, and media related misinformation's about the coronavirus disease 2019 (COVID-19) resulting in increased fear/stress related to the insufficiently known illness. The aim was to assess the influence of the COVID-19 health crisis on patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

**Methods:** A cross-sectional study on 29 adult CIDP patients was performed. The Medical Research Council scale was used to evaluate muscle strength. The degree of functional disability was measured using the Inflammatory Neuropathy Cause and Treatment disability scale. The overall quality of life (QoL) was self-estimated on a 0–100 numeric rating scale. We also used a specifically designed 22-question-survey about COVID-19.

**Results:** Regarding the COVID-19 pandemic, 62% of CIDP patients were concerned. The daily activities of 55% of patients were negatively influenced by the pandemic. During the COVID-19 outbreak, 21% of patients reported their CIDP got worse. In 39% of CIDP patients, the influence of the pandemic on CIDP therapy was reported (reducing the dose or time interval or even discontinuation). The mean value of the self-estimated QoL was  $64 \pm 19$ . Independent predictors of worse QoL were age of patients ( $\beta = -0.35$ ,  $p < 0.05$ ) and fear of the COVID-19 ( $\beta = -0.34$ ,  $p < 0.05$ ).

**Conclusion:** The COVID-19 pandemic has a significant impact on CIDP patients. Besides the direct influence of the virus and fear of the virus, restrictive measures can indirectly harm the patients with CIDP.

### 1. Introduction

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appears to be the largest pandemic of our times, and has massive impact on the healthcare systems worldwide [1]. In Serbia, from the start of the pandemic to March 2nd 2021, there have been 462,728 confirmed cases of COVID-19 with 4459 deaths. At a time of global health crisis, fear, anxiety, and stress levels increase, with common responses, such as insomnia, anxiety, frustration, fear of being infected, and loneliness [2]. The Serbian government ordered a national lockdown, during March, April and May 2020, closing educational institutions and other public services; with

recommendation for all workers to work from home if possible. The effects of protracted social isolation, massive closure of stores and a drastic reduction in the household budget also may impair people's functioning [3]. Media-related misinformation about the COVID-19 is also present globally resulting in increased fear/stress related to the insufficiently known illness [4].

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an autoimmune disease, characterized by progressive or recurrent symmetric proximal and distal weakness, sensory dysfunction, and absent or reduced tendon reflexes of all extremities, developing over at least two months [5]. CIDP can lead to many functional impairments of unpredictable duration, which may significantly affect patients'

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quality of life (QoL) even in normal circumstances [6]. Physical disability at the beginning of the disease and age are factors that influence the course and the outcome of CIDP [7]. Different factors besides physical disability, such as pain, fatigue, anxiety and depression, can affect the course and outcome of CIDP [8].

Previous studies have reported high rates of anxiety, insomnia, depression, and stress symptoms among health care workers and patients with other neurologic autoimmune diseases, such as myasthenia gravis or multiple sclerosis, during the COVID-19 pandemic [9–12]. Also, in some other neuromuscular disorders, such as amyotrophic lateral sclerosis there is an evidence of increased anxiety and depression during the COVID-19 pandemic [13]. There is a lack of data on the QoL and impact of COVID-19 pandemic on patients with CIDP during the pandemic. The current study aimed to assess the influence of the COVID-19 pandemic on patients with CIDP.

## 2. Methods

We performed a cross-sectional study during July and August 2020 (in March 2020 the first COVID-19 cases were reported in Serbia). Subjects who were called up to participate were patients with CIDP, who are regularly checked-up and treated in two tertiary healthcare centers in Serbia: the Clinical Centre Nis and the Clinical Centre of Serbia (Belgrade) which treats the majority of Serbian CIDP patients. Of 30 adult (age  $\geq 18$ ) CIDP patients who were called up to participate, 29 answered our call. Patients were assessed during their regular therapy visits or their regular check-ups. If some CIDP patients did not have regularly appointed check-ups during July and August, he/she was invited for the check-up. Only patients who fulfilled the EFNS/PNS diagnostic criteria were included [5]. Also, diagnosis of CIDP variants was made according to the EFNS/PNS criteria [5].

We collected socio-demographic and clinical data including gender, age, duration of the disease, therapeutic modality for CIDP, as well as the presence of significant comorbidities. Concomitant therapy was also noted. The Medical Research Council (MRC) 0–5 point scale (0—without movement, 5—normal strength) was used to evaluate the muscle strength [14]. The MRC sum score (MRC-SS) ranges from 0 to 60 and it comprises the following muscle groups bilaterally: shoulder abductors, elbow flexors, wrist extensors, hip flexors, knee extensors and foot dorsal flexors. MRC-SS one year before the assessment and at the time of the assessment was collected. Degree of functional disability was measured using the Inflammatory Neuropathy Cause and Treatment scale (INCAT) [15]. From the medical records, the data of INCAT score at the time of diagnosis, at nadir (the worst INCAT score obtained during the disease course) and one year before the current assessment was derived. If the patient was diagnosed less than one year before testing, we collected MRC-SS and INCAT from January and February 2020, just before the epidemic started in Serbia. Patients were also asked how they were feeling compared to the time one year ago regarding their health. The Patients' Global Impression of Change (PGIC), a 3-point verbal scale, was used to assess patients' perception of this change (i.e., 'feeling better', 'feeling same' or 'feeling worse') through time. Overall QoL was self-estimated by the patients on a numerical rating scale (NRS) from 0 to 100. For the investigation of the psychological status and emotional response of patients during the COVID-19 patients, we used a specifically designed questionnaire, consisting of 22 questions.

The study was approved by the Ethical Board of the Neurology Clinic, Clinical Centre Nis and the Neurology Clinic, Clinical Centre of Serbia. All procedures were performed in accordance with the Boards' guidelines and regulations. All participants provided written informed consent.

Data were statistically processed by the IBM SPSS statistical software (version 21) for the Windows operative system. The research results are presented in tabular and graphic form. P values of less than 0.05 were regarded as statistically significant. Numerical data were presented as percentage or mean  $\pm$  standard deviation (SD). Normality of data was

tested by the Kolmogorov–Smirnov test. For group comparisons,  $\chi^2$  test, Mann–Whitney *U* test and Student *t*-test were used, as appropriate. Correlations were assessed using Spearman's correlation coefficient. Factors that significantly correlated with lower QoL in univariate analysis ( $p < 0.05$ ) were included in the multiple linear regression analysis (enter method). Stepwise criteria were as follows: probability of F to enter variable was  $\leq 0.05$ , and probability to remove variable  $\geq 0.10$ . For all statistical tests, significant testing was two-sided, where alpha was set at 0.05 for statistical significance and at 0.01 for high statistical significance.

## 3. Results

The main socio-demographic and clinical features of our patients are presented in Table 1. Regarding the period one year ago, changes in INCAT, MRC-SS and PGIC are presented in Fig. 1.

Results obtained through the COVID-19 questionnaire are presented in Table 2. Regarding the overall concern about the impact of the COVID-19 pandemic, we found that 62.1% of patients were concerned. The main reason for patients' concern was a fear that their relatives or friends could be infected with COVID-19. Daily activities of 55.2% of patients were negatively influenced by the pandemic. The main concerns about the CIDP status were that they would experience some difficulties in drug availability, that they could not go to the hospital as usual, and that their clinical presentation will be worse because they

**Table 1**  
Socio-demographic and clinical features of CIDP patients (N = 29).

Feature	Value
Medical center - N (%)	
Clinical Center of Serbia	18 (62.1)
Clinical Center Nis	11 (37.9)
Female gender - N (%)	12 (41.4)
Age (mean $\pm$ SD, years)	48.3 $\pm$ 14.7
Disease duration (mean $\pm$ SD, months)	65.3 $\pm$ 47.1
INCAT UL at diagnosis (mean $\pm$ SD)	1.9 $\pm$ 0.8
INCAT UL at nadir (mean $\pm$ SD)	2.2 $\pm$ 0.8
INCAT UL one year ago (mean $\pm$ SD)	1.4 $\pm$ 0.9
INCAT UL at testing (mean $\pm$ SD)	1.0 $\pm$ 1.0
INCAT LL at diagnosis (mean $\pm$ SD)	2.0 $\pm$ 1.0
INCAT LL at nadir (mean $\pm$ SD)	2.2 $\pm$ 1.1
INCAT LL one year ago (mean $\pm$ SD)	1.4 $\pm$ 0.9
INCAT LL at testing (mean $\pm$ SD)	1.4 $\pm$ 1.1
INCAT overall at diagnosis (mean $\pm$ SD)	3.8 $\pm$ 1.5
INCAT overall at nadir (mean $\pm$ SD)	4.4 $\pm$ 1.6
INCAT overall one year ago (mean $\pm$ SD)	2.9 $\pm$ 1.5
INCAT overall at testing (mean $\pm$ SD)	2.4 $\pm$ 1.9
MRC-SS one year ago (mean $\pm$ SD)	51.3 $\pm$ 6.2
MRC-SS at testing (mean $\pm$ SD)	53.9 $\pm$ 6.0
CIDP variant - N (%)	
typical	19 (65.5)
atypical	10 (35.5)
EFNS/PNS NCS criteria - N (%)	
definite CIDP	22 (75.9)
probable or possible CIDP	7 (24.1)
Other diseases - N (%) <sup>a</sup>	
Present	17 (58.6)
Absent	12 (41.4)
Therapy - N (%)	
IVIg	22 (75.8)
Oral corticosteroids	10 (34.5)
Other therapy for CIDP - N (%)	
Pregabalin	8 (27.6%)
Vitamins	6 (20.7%)
Alpha-lipoic acid	1 (3.6%)

INCAT = the Inflammatory Neuropathy Cause and Treatment scale; UL = upper limbs; LL = lower limbs; MRC-SS = The Medical Research Council scale sum score; CIDP = Chronic inflammatory demyelinating polyradiculoneuropathy; NCS = nerve conduction study; IVIg = intravenous immunoglobulin.

<sup>a</sup> Other diseases in this cohort were diabetes mellitus, arterial hypertension, anemia, depression, and hypothyroidism.

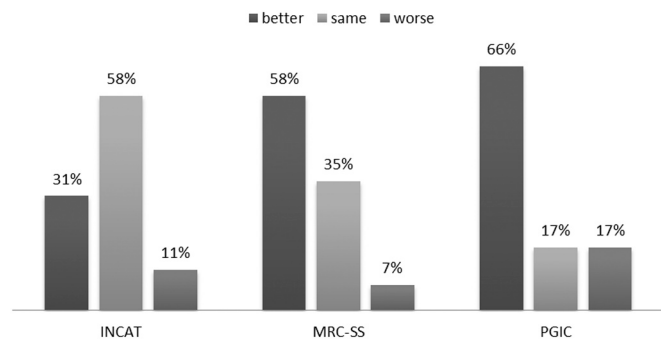


Fig. 1. Changes in INCAT, MRC-SS and PGIC regarding period one year ago.

have the concomitant disease. During the COVID-19 outbreak, 21% of patients reported their CIDP got worse. In 38.6% of CIDP patients, pandemic influenced the therapy (reducing the dose or time interval or discontinuation due to the pandemic).

Only one of our CIDP patients was infected by the SARS-CoV-2. He had a mild clinical presentation of COVID-19, was treated in home conditions, without any worsening in his CIDP status and no influence on his regular IVIg therapy.

Mean value of the self-estimated QoL on NRS was  $64.1 \pm 19.0$  of 100. In our CIDP patients QoL was associated with patients' age ( $\rho = -0.58, p < 0.01$ ), MRC-SS at the moment of testing ( $\rho = +0.44, p < 0.05$ ), and INCAT disability score at the moment of testing ( $\rho = -0.60, p < 0.01$ ). Patients with more fear of the COVID-19 had worse QoL vs. those patients without fear or with mild fear ( $54.1 \pm 16.9$  vs.  $70.3 \pm 17.9, p < 0.05$ ). All parameters that correlated with QoL in the univariate analyses were included in the multiple linear regression analysis (enter method). Independent predictors of worse QoL were age ( $\beta = -0.35, p < 0.05$ ) and fear of the COVID-19 ( $\beta = -0.34, p < 0.05$ ). Overall model was significant with adjusted  $R^2 = 0.53 (p < 0.01)$ .

#### 4. Discussion

Our results suggest the high impact of the COVID-19 pandemic on patients with CIDP. People worldwide have different degrees of fear of the COVID-19 [16,17]. In the study of psychological distress in the Chinese population during the COVID-19 outbreak, it was found that 35% of the general population experienced psychological distress [18, 19]. In accordance with our results, it was reported that the COVID-19 can specifically influence the people with chronic diseases [20]. Studies in the Spanish and Turkish populations found that those with an accompanying chronic disease were psychologically the most affected by the COVID-19 [21,22].

There are several possible reasons why CIDP patients may have pronounced psychological distress during the COVID-19 outbreak. First, it is still unknown if people with CIDP are at increased risk of developing severe clinical presentation of the COVID-19 since they are a specific group, having immune-mediated disease and receiving immunomodulatory therapy [23]. There are case reports in the current literature that suggested potential exacerbation of disease symptoms due to SARS-CoV-2 in some CIDP and myasthenia gravis patients [24,25]. Around 20% of our patients were afraid of having more severe clinical presentation of the COVID-19 since they have CIDP. The study conducted on patients with another chronic disease (diabetes mellitus) showed that the main concern of these patients (in 56% of cases) was the fear of worse clinical presentation of COVID-19 if they become infected [26]. Another important issue is that it is not known if CIDP disease course may be affected by the SARS-CoV-2. Only 17% of CIDP patients were afraid of the disease worsening during the pandemic. However, one of our CIDP patients had a mild form of the COVID-19 infection. Only larger series of CIDP patients can show if SARS-CoV-2 may affect

Table 2

CIDP patients attitudes about the COVID-19 pandemic (N = 29).

Feature	Value
Level of information about the COVID-19 pandemic – N (%)	
None	1 (3.4)
Some information	10 (34.5)
Moderate information	15 (51.7)
Excellent information	3 (10.4)
Source of information – N (%)	
State-owned television broadcasters	17 (60.4)
Other television broadcasters	9 (31.0)
Internet	9 (31.0)
Friends or relatives	6 (20.6)
Social network	3 (10.3)
Influence of the COVID-19 daily news on patient's concern - N (%)	
Not concerned	8 (27.6)
Slightly concerned	10 (34.5)
Moderately concerned	5 (17.2)
Extremely concerned	6 (20.7)
Fear of the COVID-19 pandemic – N (%)	
Not afraid	11 (37.9)
Slightly afraid	7 (24.1)
Moderately afraid	6 (20.7)
Extremely afraid	5 (17.3)
Main reason for fear or concern – N (%)	
Relatives or friends could be infected	12 (41.3)
Someone they know could die due to the infection	6 (20.6)
CIDP symptoms could be worsened	5 (16.9)
Patient could be infected	7 (24.1)
Absence of cure for COVID-19	6 (20.6)
Changes in lifestyle during and after the pandemic	2 (6.8)
Would you receive the vaccine for SARS-CoV-2? – N (%)	
Yes, after consultations with a neurologist	18 (62.1)
Yes, immediately	6 (20.6)
No	5 (17.3)
Influence of the COVID-19 pandemic on daily activities – N (%)	
No influence	14 (44.8)
Slightly negative influence	9 (34.5)
Highly negative influence	6 (20.7)
Influence of the COVID-19 pandemic on sleep quality – N (%)	
Better than before the pandemic	1 (3.4)
Same as before the pandemic	23 (79.5)
Slightly worse than before the pandemic	3 (10.3)
Much worse than before the pandemic	2 (6.8)
Check-ups at the neurologist's during the pandemic – N (%)	
No controls	11 (37.9)
Less often than usual	4 (13.9)
Same as usual	9 (31.0)
Controls were conducted via e-mail	1 (3.4)
Controls were conducted via telephone	4 (13.8)
CIDP status during the COVID-19 outbreak – N (%)	
Worse	6 (20.7)
No change	11 (37.9)
Slightly better	10 (34.5)
Much better	2 (6.9)
The main concerns about the CIDP status during the pandemic – N (%)	
Could not go to the hospital as usual	6 (20.6)
Clinical presentation of COVID-19 will be worse if they become infected	6 (20.6)
Difficulties in drug availability	9 (27.5)
CIDP could worsen during the pandemic	5 (17.2)
Weakened immune system due to CIDP drugs	3 (10.2)
If the CIDP symptoms get worse – N (%)	
Patient will try to get in contact with their neurologist	20 (68.9)

(continued on next page)

Table 2 (continued)

Feature	Value
Patient will try to get in contact with a doctor in a nearby hospital or by phone	8 (27.6)
Patient will try to get information on the Internet	1 (3.4)
The influence of the COVID-19 pandemic on CIDP therapy – N (%)	
No	17 (58.0)
Time interval between therapies was prolonged	4 (13.8)
Medication was discontinued due to the pandemic	5 (17.2)
Medication was discontinued due to the pandemic but it was previously planned	2 (6.8)
Medication was discontinued but not due to the pandemic	1 (3.4)

COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy.

the disease course. Also, reduced physical activity during the pandemic is a factor that could influence the well-being of CIDP patients. Highly negative influence of the pandemic on patient's daily activities is noticed in 20% of cases. Finally, prolonged duration of this pandemic may jeopardize the use of medical services by the patients with chronic diseases, including CIDP. In line with this, the main reason for our patients' concerns was drug availability reported by 27% and hospital accessibility reported by 20% of patients. We noted fewer neurologist check-ups in half of our patients and in as high as 41% of them therapy was changed during pandemic.

The COVID-19 pandemic has resulted in an unexpected opportunity to reexamine the need for immunomodulatory therapy in some CIDP patients. This therapy for CIDP patients is often continued by neurologist even if there is no need for that. In the PATH clinical trial, only 56% of CIDP patients treated by placebo had CIDP relapse [27]. In the study conducted by Romozzi et al., over half of patients who stopped immunomodulatory therapy did not have to restart it [28]. Accordingly, no one of our patients in which discontinuation of chronic therapy was hastened due to pandemic had disease worsening after more than five months of the follow-up. On the other hand, chronic immunoglobulin therapy may protect or reduce the risk of contracting infections, including COVID-19 so it can be useful for CIDP patients in these circumstances [29].

Anyway, continuous follow-up of these patients should be performed. During the pandemic, there is a need for establishing a balance between the risk for patients to become infected during hospital visits and adequate control of the CIDP symptoms and therapy. Check-ups should preferably be done by telemedicine or phone, but it is of note that telemedicine is neither widely available nor officially approved by the regulatory authorities in Serbia [30]. Subcutaneous immunoglobulin therapy, which could be self-administered as a home infusion, would be an adequate therapy solution [31].

Our patients reported being well informed about the COVID-19 pandemic, mostly through the state-owned media. Concern was significant among these patients, with the main concern about the potential sickness of some of their relatives or close friends. Similar results were provided in the studies conducted on patients with myasthenia gravis and relapsing-remitting multiple sclerosis [10,11].

The majority of our patients would receive a vaccine against SARS-CoV-2 immediately or after consultation with their neurologist (83%). This finding is highly encouraging, especially because there is a strong anti-vaccine campaign in Serbia as in many other countries. Also, CIDP patients may have increased fear of vaccination because they suffer from the immune-mediated disease [32].

The negative impact of the COVID-19 on self-perceived sleep quality was reported by 20% of our patients. Sleep disturbance is well recognized as a problem during the COVID-19 breakdown [33,34]. Worse sleep quality in general population, measured before and during the pandemic, is noted in 5–10% of cases [35]. Also, more than 30% of the healthcare workers during the COVID-19 reported worse sleep quality

[9,36]. Pronounced sleep disturbances were noted in myasthenia gravis patients during the COVID-19 outbreak [10].

The impact of psychological factors on patient's well-being in CIDP patients during the COVID-19 pandemic is significant. Fear of COVID-19 was the strongest predictor of worse QoL in our cohort, even stronger than muscle weakness or functional disability. The study conducted on patients with cancer showed that 'being concerned about contracting corona-virus' was correlated with lower QoL [37]. Also, persons with a serious illness quarantined because of the increased risk of infections

often report symptoms of emotional disturbance, stress, and depression [38]. For these reasons, professional psychological help and timely information are needed for chronic patients as soon as a health crisis starts.

There are several limitations of our study, such as a relatively small sample and possible intercultural difference so our results may not be easily extrapolated to other populations. We used a self-report instrument and this should be also considered as a limitation of our study. On the other hand, there is no established questionnaire for investigation of the influence of the COVID-19 pandemic on patients with neuromuscular disorders. For that purpose, we suggest that future researchers should work on establishing this kind of standardized questionnaire. The evaluation of some "pre" and "during" quarantine conditions comes from the same interview (during quarantine) so this may have biased the collection of some data. Also, longitudinal follow up during the pandemic and prolonged monitoring of CIDP patients after the pandemic is necessary for a better understanding of the influence of the COVID-19 pandemic on these patients.

In conclusion, the COVID-19 pandemic has a significant impact on CIDP patients. Fear of the COVID-19 was an independent predictor of lower QoL in CIDP patients during the pandemic. Besides the direct influence of the virus and fear of the virus, restrictive measures can indirectly harm the patients with chronic diseases, such as CIDP.

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#### CRediT authorship contribution statement

**Aleksandar Stojanov:** Investigation, Conceptualization, Writing - original draft. **Ivo Bozovic:** Conceptualization, Supervision, Writing - review & editing. **Jelena Stojanov:** Conceptualization, Methodology, Writing - review & editing. **Aleksa Palibrk:** Investigation, Formal analysis, Software. **Gordana Djordjevic:** Data curation, Validation, Writing - review & editing. **Ivana Basta:** Conceptualization, Methodology, Writing - review & editing. **Marina Malobabic:** Investigation, Formal analysis, Software. **Ana Azanjac Arsic:** Conceptualization, Supervision, Writing - review & editing. **Stojan Peric:** Conceptualization, Methodology, Writing - review & editing.

#### Disclosure statement

Authors have nothing to disclose.

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