



# COVID-19-Related Burden and Risk Perception in Individuals with Chronic Inflammatory Demyelinating Polyneuropathy and Multifocal Motor Neuropathy: A Cross-Sectional Study

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## ABSTRACT

**Introduction:** This study investigated the mental health burden of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) or multifocal motor neuropathy (MMN) during the COVID-19 pandemic in comparison to matched healthy controls.

**Methods:** The cross-sectional study included 59 patients with a diagnosis of either CIDP or MMN and 59 propensity score matched healthy controls. All participants completed a survey

including demographics, distress (distress thermometer), depressive symptoms (PHQ-2), generalized anxiety (GAD-7), COVID-19-related fear, and risk perception. Additionally, patients with CIDP or MMN were asked about the frequency and type of infections since treatment initiation.

**Results:** Patients with either CIDP or MMN reported experiencing reduced frequency or no differences in infection frequency since immune medication was initiated. Regarding COVID-19, patients with CIDP or MMN rated their risk of infection similar to healthy controls, while they expected a higher probability of the occurrence of symptoms, severe course, and dying of COVID-19. They reported increased depressive symptoms, generalized anxiety, and COVID-19-related fear in comparison to healthy controls.

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**Conclusion:** Despite their personal experience of reduced frequency of infection since immune medication was initiated, patients with CIDP or MMN reported increased risk perception and prevalence of depressive symptoms, generalized anxiety, and COVID-19-related fear in comparison to healthy controls. This highlights the need for evidence-driven strategies to protect the mental health of this vulnerable group.

**Keywords:** Chronic inflammatory demyelinating polyneuropathy; CIDP; Multifocal motor neuropathy; MMN; Anxiety; Mental health; COVID-19; SARS-CoV-2

### Key Summary Points

Patients with immune-mediated neuropathies might be particularly vulnerable in the context of the ongoing COVID-19 pandemic and thus might experience increased mental health burden.

Mental health burden and risk perception during the COVID-19 pandemic were examined in patients with chronic inflammatory demyelinating polyneuropathy (CIDP) or multifocal motor neuropathy (MMN) and compared to matched healthy controls.

Despite their personal experience of reduced frequency of infection since immune medication was initiated, patients with CIDP or MMN reported increased risk perception and mental health burden in comparison to healthy controls.

Evidence-driven strategies to protect the mental health of this vulnerable group need to be implemented.

## INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic poses an ongoing threat to public life and health. Since the first case in China in December 2019, over 308 million confirmed cases and 5 million deaths worldwide have been reported [1]. Besides respiratory tract symptoms, COVID-19 is also associated with neurological and psychological symptoms [2–5]. Patients with pre-existing chronic diseases have been shown to be at increased risk of a severe course of COVID-19 [6] and form a particularly vulnerable group in the context of the ongoing pandemic, not only from a medical but also from mental health perspective [7].

The question arises as to whether COVID-19 severity is worsened in patients treated with immunosuppressive agents and whether neurological autoimmune conditions such as chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN) are exacerbated by SARS-CoV-2 infection. In fact, cohort studies showed that the course of disease and outcomes for patients with neuroimmunological diseases seem to be ambiguous [8, 9]. While, for instance, Salter et al. [10] showed that the risk of severe outcomes from COVID-19 in individuals with CIDP was similar to that seen from the general population, other studies revealed that individuals with CIDP are at greater risk of COVID-19 infection, but also disease exacerbations and relapses due to infection with SARS-CoV-2 [11–13].

Besides the underlying pathogenesis of neuroimmunological diseases, the treatment with immunosuppressive therapies as a further vulnerability factor in patients with neuroimmunological diseases has been discussed [9, 14–16]. However, disease-modifying therapies seem—beside CD20-depleting antibodies in multiple sclerosis (MS)—not to be independent risk factors for poor COVID-19 outcomes in individuals with a neuroimmunological disease. Some studies even discussed potentially protective effects for some immunosuppressive agents against overshooting immune responses by SARS-CoV-2 infection [17]. Further risk

factors such as age, number of comorbidities, and level of disability are assumed to cause severe infection courses in patients with neuroimmunological diseases [10, 18–21].

Besides somatic strains, individuals with a neuroimmunological disease experience increased mental health burden due to diagnosis and therapy. For instance, individuals with CIDP or MMN report lower health-related quality of life [22]. Common psychological comorbidities in these patient groups are anxiety and depressive symptoms [23, 24].

The COVID-19 pandemic concerns both our physical and mental health. Vulnerable subgroups, such as patients with a neuroimmunological disease might experience further mental health deterioration due to the far-reaching cutbacks in their daily lives. Overall, the mental health burden of the general population has increased during the pandemic, and, overall, more people are reaching thresholds for mental illnesses, such as depression and anxiety, than before [25]. The impact on mental health for people with high-risk diseases [7] and mental illnesses [26] is even worse. For patients with neuroimmunological disease, preliminary research indicated increased depressive symptoms, worse sleep quality, and an increase in fatigue in comparison to healthy controls during the pandemic [27, 28]. Furthermore, disruption of healthcare services including altered treatment pathways and delayed healthcare in patients with neuroimmunological diseases due to the COVID-19 emergency is associated with worsening quality of life [29].

Despite the growing body of literature on COVID-19, little is known about the mental health burden of individuals with neuroimmunological diseases. In particular, the effect of the pandemic on the mental health burden of patients with CIDP or MMN received less attention in the scientific literature up to this point. Therefore, and given the increased vulnerability of individuals with neuroimmunological diseases during the current pandemic, the aim of the present study was to investigate the psychological impact of the COVID-19 pandemic on patients with CIDP or MMN in comparison to matched healthy controls.

## METHODS

### Participants and Procedure

The cross-sectional study was conducted on the basis of an online survey and included a total of 59 participants with a diagnosis of either CIDP or MMN and 59 matched healthy controls. The healthy controls were sampled from a large nationwide study in Germany reported in previous research [25]. Only participants who did not report any of the high-risk diseases for SARS-CoV-2 infection (diabetes, hypertension, chronic respiratory and cardiovascular diseases) were included. Data collection started on April 23 and ended on August 19, 2020. The patients were recruited by the Neurological Department of the University Hospital Essen. Eligibility requirement was adult age (at least 18 years) for all participants and a diagnosis of CIDP or MMN for the patients. Prior to participation, all participants provided written informed consent. The completion was anonymous, voluntary, and not rewarded. The Ethics Committees of the University Hospital Essen has approved the study (20-9307-BO).

### Assessment Instruments

The online survey was composed of sociodemographic items (including gender, age, relationship status, educational level, and community size). Patients with neuroimmunological disease gave information about their specific diagnosis, the experienced frequency of infections (independent of SARS-CoV-2 infections) since treatment, and the type of infection (multiple choice answer possibilities: gastrointestinal, urinary tract, flu-like, bronchopulmonary, and open-end question). Validated measurements were used to assess depressive symptoms and generalized anxiety. The Patient Health Questionnaire-2 (PHQ-2), scaled on a four-point Likert scale, was used to assess depressive symptoms [30]. Generalized anxiety symptoms were assessed by the Generalized Anxiety Disorder Scale-7 (GAD-7), scaled on a four-point Likert scale [31]. The Distress Thermometer, scaled from 0 = “no distress” to

10 = “extreme distress”, assessed participants’ distress in the past week [32]. Health status was measured by the European Quality of Life 5 Dimensions 3 Level questionnaire (EQ-5D-3L), scaled from 0 = “the worst health you can imagine” to 100 = “the best health you can imagine” [33]. Additionally, COVID-19-specific measures to assess participants’ subjective level of information about COVID-19, COVID-19-related fear, and subjective risk perception were included. All these items scaled on a seven-point Likert scale. These measures have been reported in detail in previous research [34].

### Propensity Score Matching (PSM)

PSM seeks to remove the impact of observed confounding variables to estimate the effect of the variable of interest—in our case the neuroimmunological diagnosis—by ensuring that both groups (patient group vs. control group) have similar distributions of baseline covariates [35]. The large German population-based community sample ( $N = 18,285$ ) was used as basis for the healthy control group. Matching was based on the following covariates: gender, age, education, relationship status, and community size. Also, people with mental illness were excluded from the reference sample since none of the patients in the treatment group indicated being diagnosed with mental diseases, either. We ensured that covariates and propensity scores were balanced across both groups: all standardized mean differences were smaller than 0.1, which is recommended for estimating differences in means [36] (see supplemental online material for detailed balance diagnostics). The propensity scores showed a large overlap between the two groups (CIDP/ MMN:  $N = 59$ ,  $M = 0.19$ ,  $SD = 0.20$ ,  $Mdn = 0.12$ ; controls:  $N = 59$ ,  $M = 0.18$ ,  $SD = 0.19$ ,  $Mdn = 0.12$ ). Further analysis was based on this new matched sample.

### Statistical Analyses

Matching was conducted using the R package MatchIt [37]. Further data analysis was done using SPSS Statistics 25 (IMB, Armonk, NY,

USA). As the Kolmogorov–Smirnov test revealed that data were not normally distributed, non-parametric alternatives were performed. To identify differences in mental health burden, COVID-19-related fear, subjective level of information, and subjective risk perception between individuals with neuroimmunological disease and controls, Mann–Whitney  $U$  tests were performed. Here, Cliff’s delta was added as an effect size. Fisher’s exact test was applied to examine differences in proportion in the categorical variables. The level of significance was set at  $\alpha = 0.05$  (two-sided tests).

## RESULTS

### Participant Characteristics

Of the individuals with a diagnosis of either CIDP or MMN ( $n = 59$ ), 42.4% were female and 59.3% ( $n = 25$ ) were aged between 55 and 74 years. Of the healthy controls, 42.4% ( $n = 25$ ) were female and 59.3% ( $n = 25$ ) were aged between 55 and 74 years. Participant characteristics and medical data are shown in Table 1.

### Frequency and Type of Infection Since Treatment

Of the individuals with a diagnosis of CIDP or MMN, 4.0% ( $n = 2$ ) reported more frequent infections since medication, 40.0% ( $n = 20$ ) reported less frequent infections, and 56.0% ( $n = 28$ ) reported no difference in frequency of infection (Fig. 1). Among the patients, 6.0% ( $n = 3$ ) suffered from gastrointestinal infection, 12.0% ( $n = 6$ ) reported urinary tract infection, 54.0% ( $n = 27$ ) were affected by flu-like infection, and 20.0% ( $n = 10$ ) reported bronchopulmonary infection. For 15.3% ( $n = 9$ ) of the patients, data regarding infection was missing (Fig. 2). Intravenous immunoglobulins (IVIg) were administered to 66.0% ( $n = 33$ ) of the patients and 10.0% ( $n = 5$ ) received subcutaneous immunoglobulin (SCIg).

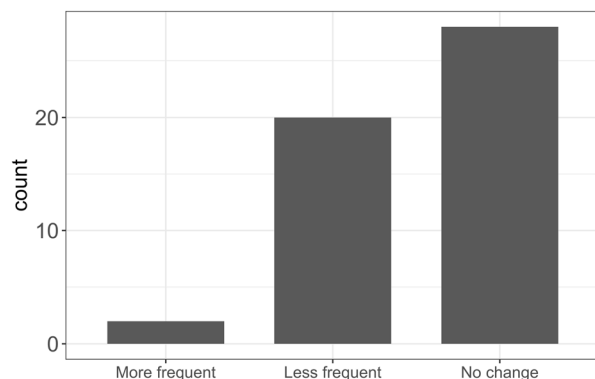
**Table 1** Sociodemographic and medical characteristics

	Healthy controls, <i>n</i> (%)	Patients with CIPD or MMN, <i>n</i> (%)	<i>p</i>
<i>n</i>	59	59	
Gender: female	25 (42.4)	25 (42.4)	1.000
Age, years			1.000
18–24	1 (1.7)	1 (1.7)	
25–34	1 (1.7)	1 (1.7)	
35–44	2 (3.4)	2 (3.4)	
45–54	9 (15.3)	9 (15.3)	
55–64	15 (25.4)	15 (25.4)	
65–74	20 (33.9)	20 (33.9)	
75–84	10 (16.9)	9 (15.3)	
85+	1 (1.7)	2 (3.4)	
Education			0.992
University degree	18 (30.5)	18 (30.5)	
High school degree	15 (25.4)	14 (23.7)	
Realschule (secondary degree)	13 (22.0)	15 (25.4)	
Hauptschule (secondary degree)	9 (15.3)	8 (13.6)	
Other	4 (6.8)	4 (6.8)	
Community size			0.927
Metropolis	28 (47.5)	30 (50.8)	
Medium-sized city	24 (40.7)	22 (37.3)	
Small town	4 (6.8)	3 (5.1)	
Rural area	3 (5.1)	4 (6.8)	
Relational status: in relationship	51 (86.4)	51 (86.4)	1.000
Infection since medication			
More often		2 (4.0)	
Less often		20 (40.0)	
No change in infection frequency		28 (56.0)	
Bronchiopulmonary infection: yes		10 (20.0)	
Gastrointestinal infection: yes		3 (6.0)	
Flu-like infection: yes		27 (54.0)	
Urinary tract infection: yes		6 (12.0)	

### Subjective Risk Perception Regarding COVID-19

The results of the Mann–Whitney *U* tests revealed no significant difference between patients with CIPD or MMN and controls concerning the subjective risk perception of infection with COVID-19 ( $W = 1960.5$ ,  $p = 0.233$ ).

However, in comparison to healthy controls they reported a significantly higher subjective risk of the occurrence of symptoms,  $W = 2193.5$ ,  $p = 0.014$ ,  $\delta = 0.260$ ; a severe course,  $W = 2506.0$ ,  $p < 0.001$ ,  $\delta = 0.440$ ; and dying of COVID-19,  $W = 2406.0$ ,  $p < 0.001$ ,  $\delta = 0.382$  (Fig. 3).



**Fig. 1** Infection frequency since medication in patients with CIDP or MMN.  $N = 50$ . Data regarding infection was missing for  $n = 9$  of the patients with CIDP or MMN

### Generalized Anxiety, Depressive Symptoms, and Distress

The results of the Mann–Whitney  $U$  tests revealed significant differences between patients with either CIDP or MMN and healthy controls with regard to generalized anxiety,  $W = 2274.0$ ,  $p = 0.004$ ,  $\delta = 0.307$ , and depressive symptoms,  $W = 2225.5$ ,  $p = 0.005$ ,  $\delta = 0.279$ . For all details, see Fig. 4.

More specifically, 32.2% of the individuals with CIDP or MMN (vs. 13.6%) reported mild symptoms, 20.3% (vs. 6.8%) moderate symptoms, and 3.4% (vs. 8.5%) severe generalized anxiety symptoms compared to the healthy controls. With regard to depressive symptoms, 15.3% of the individuals with CIDP or MMN and 8.5% of healthy controls reported scores above the cutoff. For elevated distress, 59.3% of the patients with CIDP or MMN and 49.2% of healthy controls reached a score above the cutoff (Table 2).

### COVID-19-Related Fear and Subjective Level of Information

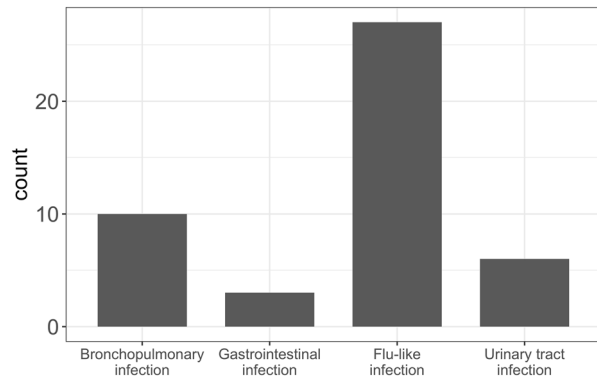
Compared to the healthy controls, patients with CIDP or MMN reported significantly more COVID-19-related fear,  $U = 2100.5$ ,  $p = 0.048$ ,  $\delta = 0.207$ . Both groups reported feeling equally well informed about COVID-19 (Fig. 4).

## DISCUSSION

The present study examined the mental health burden of individuals with immune-mediated neuropathies in comparison to matched healthy controls during the COVID-19 pandemic. We assumed individuals with a neuroinflammatory disease to be particularly vulnerable to the mental health effects of the current pandemic. The results are in line with this hypothesis as individuals with a diagnosis of either CIDP or MMN reported increased COVID-19-related fear, generalized anxiety, and depressive symptoms compared to matched healthy controls. However, this psychological burden might not be driven by the personal experience of increased infection as patients reported that they experienced no changes or even a decrease in infection frequency since medication was initiated. Most patients (66.0%) received intravenous immunoglobulins (IVIg) and the most common reported type of infection was the common cold.

Despite the growing body of literature on COVID-19, the effect of the pandemic on the mental health burden of patients with CIDP or MMN has received less attention thus far. To the best of our knowledge, we were the first to conduct a study of patients with CIDP or MMN in direct comparison to healthy controls during the pandemic. Stojanov et al. [13] reported not only a direct effect of COVID-19 but also an indirect effect on patients with CIDP; 62% of the patients reported concerns, 55% a reduction of daily activities, and 39% an influence on their CIDP therapy. These concerns and changes in daily life and treatment could explain why the present sample showed increased COVID-19-related fear, depressive symptoms, and anxiety.

Overall, for individuals with CIDP or MMN, as well as the healthy control group increased prevalence of depressive symptoms and generalized anxiety compared to previously published studies was found, suggesting an overall increased mental health burden [38]. For instance, 9–12.1% of patients with CIDP reached clinically significant scores for depression [22, 39] whereas 15.3% of the present

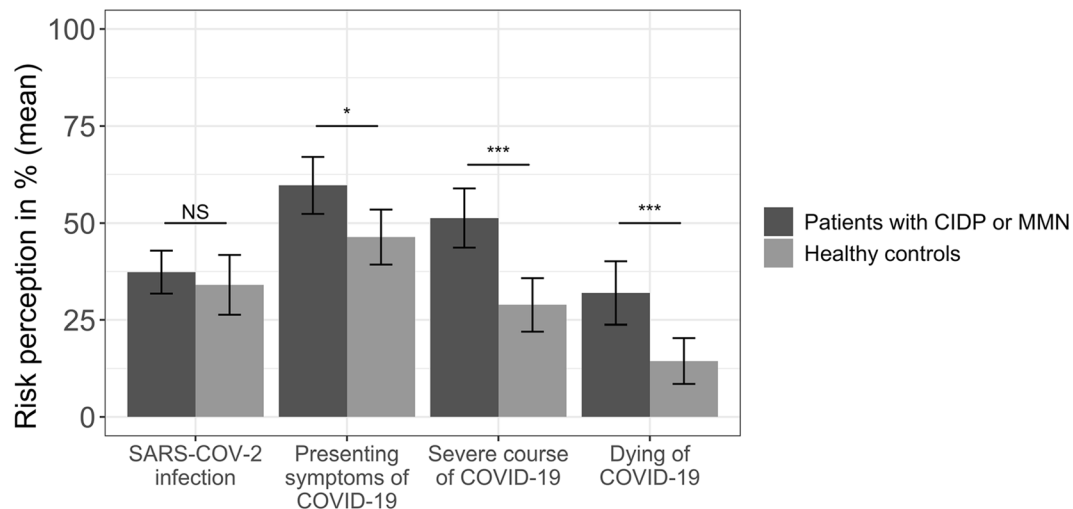


**Fig. 2** Type of infection since medication in patients with CIDP or MMN. *N* = 50. Data regarding infection was missing for *n* = 9 of the patients with CIDP or MMN

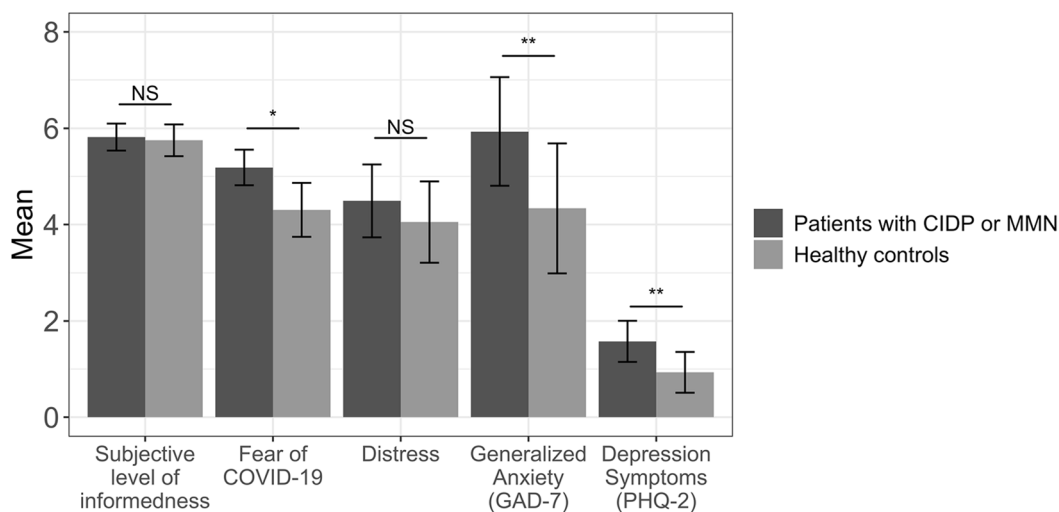
sample reported major depression symptoms. The results in this study are in line with previous research, reporting increased prevalence of depression and generalized anxiety during the pandemic in the general German population [25], and in risk groups such as individuals with diabetes [34]. Deterioration in mental health during the pandemic was also observed in individuals with myasthenia gravis (MG) and MS. Individuals with MG experienced a rise in depression, anxiety and insomnia, and reduced

quality of life [40, 41]. Compared to healthy controls, individuals with MS reported higher psychological strain. However, longitudinal studies show that these differences might be due to the mental health burden that already existed before the pandemic [42].

Patients with a diagnosis of CIDP or MMN reported increased COVID-19-related fear compared to the healthy controls. This could be a consequence of the risk perception reported by this patient group. Most patients reported that they experienced no increased frequency of infection since medication was initiated, and a substantial proportion even experienced a decrease in infection frequency. Accordingly, regarding COVID-19, the patients rated their expected probability of infection similar to controls. However, they expected a significantly higher probability of the occurrence of symptoms, a severe course, and dying of COVID-19. This perception, which is in contrast to the actually reduced experienced decrease in infection frequency, might arise from the fact that at the beginning of the COVID-19 pandemic the population was informed that individuals with pre-existing health conditions were more likely to show severe courses of COVID-19 infection and a higher risk of a fatal course [43, 44]. Also, from a psychological perspective, the



**Fig. 3** Subjective risk perception in comparison between neuroimmunological patients and healthy controls. \**p* < 0.05, \*\**p* < 0.01, \*\*\**p* < 0.001; error bars, 95% CI



**Fig. 4** Comparisons between patients with a CIDP or MMN diagnosis and healthy controls. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ ; error bars, 95% CI. *GAD-7*

Generalized Anxiety Disorder Scale-7, *PHQ-2* Patient Health Questionnaire-2, *DT* distress thermometer

discrepancy between experienced risk reduction and increased risk perception with regard to COVID-19 could be explained by fear of the potential consequences of infection rather than their experience alone.

The strength of the present study is that it examined the mental health burden of individuals with a neuroinflammatory disease during the COVID-19 pandemic in comparison to matched healthy controls. However, some limitations need to be acknowledged. As a result of the cross-sectional design, no causality can be inferred. Further, the study results are based on self-reports. Thus, no objective verification is possible. Data was collected via an online survey, so selection bias needs to be considered when interpreting the results. Similarly, recall bias could not be ruled out entirely. Comorbid health conditions were not examined for the individuals with CIDP or MMN, which might impact the generalizability of the findings. Further, the beginning of the survey was conducted during the early lockdown phase in Germany which included the closure of public facilities and contact bans. At the end of April, the wearing of face masks in public places became mandatory. During the survey period, the measures were gradually eased. Thus,

generalizability might be limited given these constraints on social interactions during the early days of the pandemic.

To summarize, the ongoing COVID-19 pandemic has a significant impact on the population and particularly on people with pre-existing health conditions such as an immune-mediated neuropathies. Increased prevalence of depressive symptoms, generalized anxiety, and COVID-19-related fear in patients with CIDP or MMN highlights the need for evidence-driven strategies to protect and improve mental health of vulnerable groups, such as patients affected by chronic diseases, during the ongoing pandemic. Mindfulness and skill-based e-mental health interventions like “CoPE It” have been shown to successfully reduce distress, depression, and anxiety in the general population during the COVID-19 pandemic [45]. Such programs could be adapted towards the needs of individuals with CIDP or MMN and deliver psychological interventions in a flexible way. Compared to healthy controls, patients with either CIDP or MMN reported increased risk perception and mental health burden despite their personal experience of reduced frequency of infection since immune medication was initiated. The exact determinants are still unclear



**Table 2** Prevalence of generalized anxiety, depressive symptoms, and distress in patients with CIDP or MMN and in healthy controls

	Patients with CIDP or MMN, <i>n</i> (%)	Healthy controls, <i>n</i> (%)	<i>p</i>
<i>n</i>	59	59	
Depression (PHQ-2)			
No depression	50 (84.7)	54 (91.5)	0.393
Depression	9 (15.3)	5 (8.5)	
Generalized anxiety (GAD-7)			
No anxiety	26 (44.1)	42 (71.2)	0.003
Mild anxiety	19 (32.2)	8 (13.6)	
Moderate anxiety	12 (20.3)	4 (6.8)	
Severe anxiety	2 (3.4)	5 (8.5)	
Distress			
No distress	24 (40.7)	30 (50.8)	0.356
Distress	35 (59.3)	29 (49.2)	

*GAD-7* Generalized Anxiety Disorder Scale-7, sum scores of  $\geq 5$ ,  $\geq 10$ , and  $\geq 15$  indicate mild, moderate, and severe generalized anxiety symptoms, respectively, *PHQ-2* Patient Health Questionnaire-2, sum scores of  $\geq 3$  indicate major depression symptoms, *DT* distress thermometer, scores of  $\geq 4$  indicate elevated distress

and further research on this vulnerable group is needed.

## CONCLUSION

Patients with immune-mediated neuropathies reported an increased risk perception and mental health burden in comparison to healthy controls. Evidence-driven strategies to protect the mental health of this vulnerable group should be implemented and must be tailored to

the disease-specific needs of this patient group. Mental healthcare needs to be accessible even in times of contact restrictions and increased risk of infections.

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**Author Contributions** Venja Musche, Alexander Bäuerle and Lisa Jahre made substantial contributions to the study's design, actively participated in the acquisition of data, statistical analysis, and interpretation of data, and prepared the manuscript. Adam Schweda, Hannah Dinse, Sheila Moradian, Benjamin Weismüller and Madeleine Fink actively participated in the interpretation of data and edited the manuscript. Anna Wolters, Michael Fleischer and Christoph Kleinschnitz made substantial contributions to the study's conception and revised the manuscript critically. Martin Teufel, Eva-Maria Skoda and Mark Stettner made substantial contributions to the study's conception and design, actively participated in the interpretation of data, and revised the manuscript critically for important intellectual content. All authors have read and agreed to the final manuscript.

**Disclosures** Venja Musche, Alexander Bäuerle, Lisa Jahre, Adam Schweda, Hannah Dinse, Sheila Moradian, Benjamin Weismüller, Madeleine Fink, Anna Wolters, Michael Fleischer, Christoph Kleinschnitz, Martin Teufel, Eva-

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**Compliance with Ethics Guidelines** All participants gave written informed consent. The study was approved by the Ethics Committees of the University Hospital Essen (20-9307-BO).

**Data Availability** The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

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