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COVID-19 in a Neuroimmunological Outpatient Cohort: The Bernese Experience

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Abstract: The COVID-19 pandemic specifically affects the management and treatment of patients with autoimmune neurological disorders. Major concerns include potentially higher risks of infection or severe disease course under certain immunotherapies used to treat those disorders and the influence of COVID-19 on the underlying disease. We present data of the neuroimmunological outpatient department of the University Hospital of Bern (Switzerland). 24 cases were analyzed, 19 of them suffered from Multiple Sclerosis. Of these 24 patients, 6 were hospitalized, 2/6 were treated in the Intensive Care Unit. Possible risk factors for severe course (defined as need for hospitalization) observed in our cohort included cardiovascular risk factors, treatment with B-cell depleting agents, Sphingosine-1 Phosphate Receptor Modulators, and oral steroid therapies. These data are based on a small, retrospective observational cohort and should be interpreted with caution, although they are in line with several other cohort studies.

Keywords: COVID-19; SARS-CoV-2; multiple sclerosis; NMOSD; Myasthenia Gravis; immunotherapies

1. Introduction

COVID-19 caused by SARS-CoV-2 substantially impacts surveillance and treatment of people with autoimmune neurological disorders like Multiple Sclerosis (MS). Since most of the treatments, herein referred to as immunotherapies, change function and constitution of the immune system, questions about infectious risks of these agents in times of COVID-19 arise. The evidence on these topics has previously been sparse, and to a certain degree still is today. Early registry studies in MS and rheumatological patient cohorts during the pandemic identified possible factors enhancing morbidity, namely age, male sex, B-cell depleting- and steroid therapies [1–5]. Our retrospective study, using the international, open-access database "FDA Adverse Events Reporting System" (FAERS) and including data on the course of the pandemic and the abilities of the respective healthcare systems, demonstrated age, male sex and B-cell depleting therapies as mortality risk enhancing factors [6]. Larger efforts such as the Neuro-COVID registry "EAN NEuro-COVID ReGistrY Consortium" (ENERGY) of the European Academy of Neurology (EAN) and the "Lean European Open Survey on SARS-CoV-2 infected patients" (LEOSS)-registry [7,8], in which Bern alongside with several Swiss and German centers participated, are ongoing [9,10]. The aim of the data presented here is to demonstrate the impact of COVID-19 on a university neuroimmunological outpatient department, to describe risk factors (with regard to patients and in relation to immunotherapy) and the short-term impact of COVID-19 on the underlying disorder.

2. Materials and Methods

This single-center, observational, retrospective cohort study of patients from the Bern University Hospital neuroimmunological outpatient department includes male and female adult patients with any neuroimmunological disease with PCR-confirmed infection

with SARS-CoV-2 between March 2020 and May 2021. Anecdotal cases without PCR confirmation (*n* = 3), and cases with missing information (*n* = 2) were excluded. The development of anti-SARS CoV-2 antibodies in COVID-19 patients treated with B-cell depleting therapies was recently described using this cohort by Friedli et al. [11].

Data were analyzed with SPSS © Statistics 25 (IBM Armonk, New York, NY, USA, 2017). Figures were prepared with Graphpad Prism 8 (San Diego, CA, USA, 2018). All patients gave written informed consent to participate in the neuroimmunological registry (KEK BE 2017-01369).

3. Results

3.1. Patient Cohort

This cohort consists of patients from within the Bern University Hospital (Switzerland) neuroimmunological outpatient department (*n* = 24). The mean age of our patients is 45.0 years (Range: 25–67, 95%-confidence interval (95% CI): 40.1–49.8) with 17/24 being female. Most patients in our cohort suffer from MS (*n* = 19), mostly of a relapsing-remitting phenotype (*n* = 17), Myasthenia Gravis (MG, *n* = 2), Neuromyelitis-Optica Spectrum Disorder (NMOSD, *n* = 1), Behçet's Disease (*n* = 1) and one case of "Progressive Encephalomyelitis with Rigidity and Myoclonus" (PERM, *n* = 1). Within the MS and NMOSD subcohort, the mean Extended Disability Status Scale (EDSS) before COVID-19 was 2.4 (95% CI: 1.3–3.5; range 0–7). 8/24 of patients were, at the timepoint of their infection, treated with B-cell depleting agents (Ocrelizumab 6/24 and Rituximab 2/24), followed by Sphingosine-1 Phosphate Receptor Modulators (S1PRM, Fingolimod 4/24 and Ozanimod 1/24); the other immunotherapies are listed in Table 1. Prednisolone is used in 2 patients, in conjunction with Azathioprine or Rituximab, respectively, at a Prednisolone dose of 5 mg/day.

Table 1. Characteristics of our patient cohort.

Category	Subcategory	*n*
Sex	Male	7/24
	Female	17/24
Age		Mean 45.2 (Range: 25–67, 95% CI: 40.2–50.3)
Diagnosis	MS	19/24
	RRMS	17/19
	SPMS	1/19
	PPMS	1/19
	MG	2/24
	NMOSD	1/24
	Neuro-Behçet's Disease	1/24
	PERM	1/24
Disability Status (MS- and NMOSD patients)		Mean EDSS 2.4 (Range: 0–7.0, 95% CI 1.3–3.5)
Immunotherapy	No immunotherapy	4/24
	Azathioprine	2/24
	Prednisolone [1]	2/24
	Dimethyl Fumarate	2/24
	IFN-Beta	1/24
	IVIG	1/24
	Fingolimod	4/24
	Natalizumab	1/24
	Ocrelizumab	5/24
	Ozanimod	1/24
	Rituximab	2/24
Cardiovascular Risk Factors [2]		11/24

Abbreviations: EDSS: Extended Disability Status Scale, RRMS–relapsing-remitting Multiple Sclerosis (MS), SPMS: secondary-progressive MS, PPMS: primary-progressive MS, NMOSD: Neuromyelitis Optica Spectrum Disorder, MG: Myasthenia Gravis, PERM: Progressive Encephalomyelitis with Rigidity and Myoclonus. [1] In conjunction with Azathioprine and Rituximab in 1 case, each. Dose in both cases 5 mg/day. [2] Cardiovascular Risk Factors: Arterial Hypertension (4/24), Dyslipidemia (3/24), Diabetes Mellitus Type 2 (3/24), Obesity (3/24), Smoking (4/24), more than one might be present.

Concomitantly, 11/24 patients presented with cardiovascular risk factors, including arterial hypertension (4/24) and diabetes mellitus type 2 (3/24). Cardiovascular risk factors are present in 4/6 of the hospitalized patients.

3.2. COVID-19 Course

Following the course of the pandemic, most SARS-CoV-2 infections occurred between September 2021 and February 2022 (19/24; see Figure 1), when most infections in Switzerland also occurred [12].
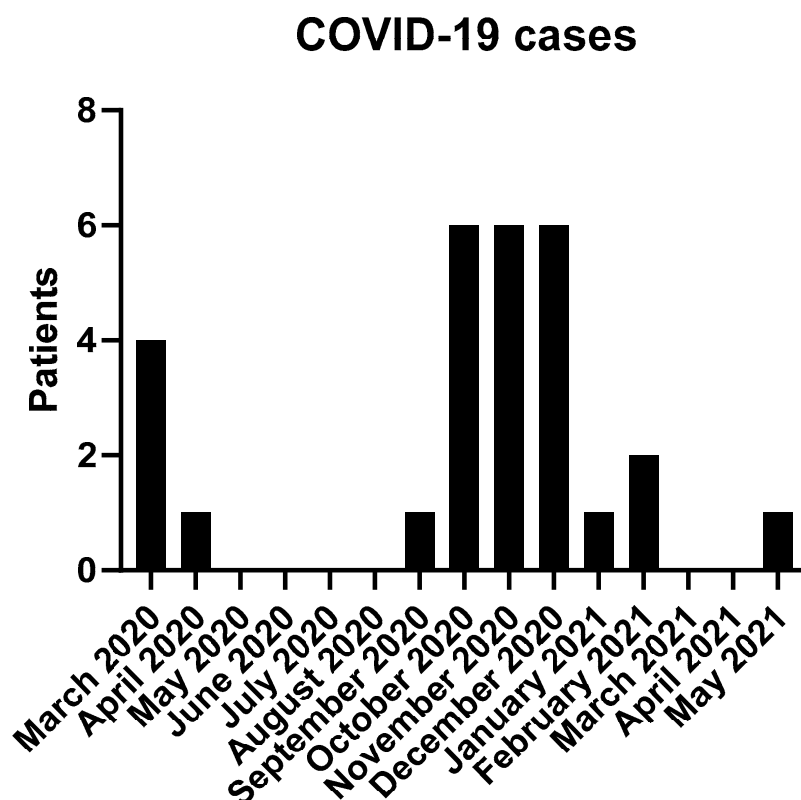

Figure 1. Showing the COVID-19 cases per month of our cohort.

In 18/24 cases, the disease course was mild with patients being managed in an outpatient setting and with symptomatic treatment only, if any. No deaths were observed, but 6/24 patients were hospitalized. One MS patient (treated with Fingolimod) and one MG patient (treated with Rituximab plus Prednisolone) suffered from viral Acute Respiratory Distress Syndrome (ARDS) and both were transferred to an Intensive Care Unit (ICU). The antiviral drug Remdesivir [13] was administered in 2 cases (in one hospitalized- and in one ICU patient) and Dexamethasone in 3 (in two ICU patients and one hospitalized patient) in conjunction with supplementary oxygen [14] (see Table 2). Within the six hospitalized patients, three were treated with B-cell depleting agents (1/3 Rituximab, 1/3 Ocrelizumab, 1/3 Rituximab plus Prednisolone), two with S1PRM (Fingolimod and Ozanimod *n* = 1 each) and one with Azathioprine plus Prednisolone for their underlying autoimmune disorder.

3.3. Influence of COVID-19 on Underlying Disease

Since our cohort mainly consists of MS patients, we will briefly discuss the impact of COVID-19 on their underlying disease. One relapse post COVID-19 occurred in a patient with paused immunotherapy (treated before with Dimethyl Fumarate, but paused due to lymphopenia). Optic neuritis without other radiographic evidence of disease activity occurred 19 days after the PCR diagnosis of COVID-19 and was treated with a reduced dose of intravenous Methylprednisolone (500 mg/3 days) upon resolution of COVID-19

symptoms and inflammatory blood markers. The pre-COVID-19 EDSS within our MS and NMOSD cohort was 2.4 (95% CI 1.3–3.6) and there was no significant difference to the post-COVID-19 EDSS of 2.5 (1.3–3.7; $p = 0.7$, Wilcoxon Signed Rank Test). Radiologically, new or enlarging T2-lesions on cranial MRI (cMRI) post-COVID was present in 3/10 of all RR-MS patients (no contrast enhancing lesions). We compared this MRI activity with the two preceding MRI pre-COVID ($n = 10$ patients with MRI post-COVID, 9/19 had no new cMRI to date). Here 0/19 had new/enlarging T2-lesions, but the differences to the post-COVID MRI were not statistically significant ($p = 0.1$; Wilcoxon Signed Rank Test). Clinically, 5/24 patients reported at least transiently a worsening of their underlying disease symptoms after COVID-19 (worsening of diplopia in 1/2 MG patients, fatigue and increase in motor disability in 5/18 MS patients).

Table 2. COVID-19 course, outcomes and specific treatments.

Category	Subcategory	*n*
Symptoms	General condition deterioration	18/24
	Fever	14/24
	Dyspnea	3/24
	Anosmia	7/24
	Pneumonia	2/24
	ARDS	2/24
	Death	0/24
Care Setting	Outpatient	18/24
	Inpatient	4/24
	ICU	2/24
COVID-19 treatment	Remdesivir and Dexamethasone	2/24
	Dexamethasone	3/24

Abbreviations: ICU: Intensive Care Unit, ARDS: acute respiratory distress syndrome.

4. Discussion

We here present data of COVID-19 cases of a university neuroimmunological outpatient department in Switzerland. While most of the infections with SARS-CoV-2 had a mild to moderate course, six of 24 patients needed to be hospitalized, two suffered from viral ARDS and were treated in the ICU, but no patient died. In this observational, retrospective analysis, we could demonstrate classical risk factors for a severe COVID-19 course, especially cardio-vascular risk factors [15], as 4/6 patients that needed to be hospitalized had at least one of them, additionally half of the hospitalized patients were treated with B-cell depleting therapies. Viewing the immunosuppressive mode of action of these therapies, the pivotal trial data and emerging data on COVID-19 [2,6,16], our data are well in line. In cohort studies in rheumatology [16] and in MS [2], steroid use, long-term and short-term, e.g., in case of an MS relapse, is associated with a poorer COVID-19 course. In our cohort, both prednisolone-treated patients needed to be hospitalized, one in ICU; yet, both received immunosuppressive co-treatments. The influence of an infection with SARS-CoV-2 on the underlying autoimmune disorder is unclear, and to date there are no published larger studies in this regard. Infections are known triggers of MS relapses [17,18], in case of COVID-19, this needs to be further investigated. In our cohort, one relapse (optic neuritis) occurred after COVID-19 in a patient with paused immunotherapy. In the absence of a control group, we cannot compare the actual incidence of relapses in this period. In the short-term (<12 months), no influence of an infection with SARS-CoV-2 on disability progression was detectable, but its influence on long- and medium-term MS disease course is still unclear.

Since these results are based on a small, retrospective cohort, we are cautious about how we interpret these data and well aware of the biases of an observational registry. Statistical adjustments and regression analyses are not possible due to a limited number of patients. We consider these data, although well in line with other studies, more a report from direct patient care experience. As an outlook for the upcoming months, additional

issues will arise, concerning, e.g., vaccine hesitancy in neuroimmunological patients [19], vaccine efficacy in the context of immunotherapies, and questions of booster vaccinations in immunocompromised patients [20] as well as the use of anti-spike protein antibody cocktails in patients at risk [21].

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