DOI: https://doi.org/10.20513/2447-6595.2024v64n1e83250

ORIGINAL ARTICLE

Vaccination for COVID-19 in patients with multiple sclerosis: sociodemographic aspects, safety and associated psychological factors

Vacinação para COVID-19 em pacientes com esclerose múltipla: aspectos sociodemográficos, segurança e fatores psicológicos associados

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ABSTRACT

Objectives: To describe clinical-sociodemographic characteristics of patients with multiple sclerosis (MS) vaccinated against COVID-19, evaluating clinical worsening after vaccination and factors associated with vaccine refusal. **Methods:** This is a cross-sectional observational study with application of a structured form in patients with MS from Hospital Universitário Walter Cantídio addressing clinical, sociodemographic and psychological factors related to vaccination against COVID-19. Data were tabulated and described using means with standard deviation and frequency/proportion. Statistical analysis was performed adopting statistical significance of 5%. **Results:** Fifty-one patients (76.4% women) were evaluated, mean age 43.3 years (18-72). Of these, 29 (57%) had mild side effects and 7 had COVID-19 after vaccination. There was no significant increase in the annualized rate of relapses or expanded disability status scale. Twelve patients reported fear regarding vaccination, with intentional delay in 5 patients. The main sources of fear mentioned were social networks, television and friends/family. **Conclusions:** In this study, vaccination for COVID-19 in patients with multiple sclerosis proved to be safe, not leading to relapses or functional worsening after vaccination. The fear of vaccinating led to delay in some patients, and social networks were the main source of fear.

Keywords: Multiple Sclerosis. COVID-19. Vaccination. Vaccines.

RESUMO

Objetivos: Descrever características clínicas-sociodemográficas de pacientes com esclerose múltipla (EM) vacinados contra COVID-19, avaliando piora clínica após vacinação e fatores associados com a recusa vacinal. **Metodologia:** Trata-se de estudo observacional transversal com formulário estruturado em pacientes com EM do Hospital Universitário Walter Cantídio abordando aspectos clínicos, sociodemográficos e fatores psicológicos relacionados à vacinação contra COVID-19. Os dados foram tabulados e descritos através de médias com desvio-padrão e frequência/proporção. Análise estatística foi realizada adotando significância estatística de 5%. **Resultados:** Foram avaliados 51 pacientes (76,4% mulheres), idade média 43,3 anos (18-72). Desses, 29 (57%) apresentaram efeitos colaterais leves e 7 tiveram COVID-19 após vacinação. Não houve aumento significativo da taxa anualizada de surto ou escala de status de incapacidade expandida. Doze pacientes relataram medo referente à vacinação, com atraso intencional em 5 pacientes. As principais fontes de medo citadas foram redes sociais, televisão e amigos/familiares. **Conclusões:** Neste estudo, a vacinação para COVID-19 em pacientes com EM mostrou-se segura, não levando a surtos ou piora funcional pós-vacinação. O medo de vacinar-se levou a atraso em alguns pacientes, sendo as redes sociais as principais fontes de medo.

Palavras-chave: Esclerose Múltipla. COVID-19. Vacinação. Vacinas.

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Conflict of interests: Não há qualquer conflito de interesses por parte de qualquer um dos autores.
Received: 29 Jan 2023; Revised: 11 Ago 2023; Accepted: 08 Nov 2023.

INTRODUCTION

Multiple sclerosis (MS) is the most common demyelinating disease of the central nervous system,[1] with an estimated prevalence of 2.5 million people worldwide.[2] In Brazil, the prevalence has been estimated in 8.69/100,000 inhabitants.[3] Patients can recover clinically from acute demyelination attacks, presenting the classic disease course of relapses (periods in which the disease manifests itself) and remissions.[2]

The acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) was initially reported in December 2019 and is responsible for the COVID-19 disease, which is still pandemic in 2022.[4] According to the World Health Organization (WHO), by December/2022 more than six hundred million cases of COVID-19 have been reported worldwide, with more than six million deaths reported from the disease.[5] Only in Brazil, more than 35 million cases have been reported, with more than 692.000 deaths resulting from SARS-CoV-2 infection.[4]

Vaccines for COVID-19 have changed and continue to change the way the disease evolves since their introduction in late 2020.[6] One of the most significant differences in the development of a COVID-19 vaccine is the wide range of technology platforms used.[7] The BNT162 vaccine (Pfizer®-BioNTech®) became the first licensed product and since then several other vaccines with different technologies have been launched.[8] In December 2022, the vaccines distributed to the population in Brazil are: Adsorbed COVID-19 inactivated vaccine (Butantan®/Sinovac® and CoronaVac-Sinovac®), ChAdOx1-S (AstraZeneca®/Fiocruz®), BNT162 (Pfizer®/BioNTech®) and Ad26.COV2.S (Janssen®).[6]

With the COVID-19 pandemic, there was concern about new episodes of MS relapses triggered by COVID-19, as well as the fear of the reactions that the several vaccines developed could cause in patients with MS.

There are studies evaluating the evolution of MS patients who have been vaccinated for COVID-19, reporting whether the vaccines are effective, stimulate humoral immunogenicity or can be triggers for clinical worsening or new relapses of the disease.[9] However, few studies included the Covid-19 Inactivated Adsorbed Vaccine (Butantan®/Sinovac® and CoronaVac-Sinovac®), the first vaccine used in Brazil, in the clinical course of MS.

The aim of this study is to describe the sociodemographic and clinical characteristics of patients with MS vaccinated with the several COVID-19 vaccines available in Brazil, evaluating clinical worsening or new relapses after vaccination. Psychological factors associated with the fear of vaccination against COVID-19 will also be evaluated, considering possible interference of anti-vaccine campaigns.

METHODS

This cross-sectional observational study was conducted with patients with a previous diagnosis of MS who were vaccinated against COVID-19 and who were followed in the outpatient clinic of demyelinating diseases of a tertiary hospital in northeastern Brazil (Hospital Universitário Walter Cantídio - Fortaleza/CE).

All patients with MS who met the revised McDonald's 2017 criteria were invited to answer a structured form, from March to October 2022, being asked about sociodemographic data, clinical aspects related to MS (disease type, year of diagnosis, current and previous treatment, expanded disability status scale [EDSS] and relapses rate), vaccination status against COVID-19 (addressing what type of vaccine, how many doses, side effects, occurrence or not of new relapses of MS and COVID-19 after vaccination) and psychological factors related to vaccination.

The questionnaires were completed during outpatient consultations in person and by voice calls remotely.

The study was approved by the local Research Ethics Committee with the number 56531422.7.0000.5045 (report number 5317582).

Statistical analysis

Descriptive analysis was performed using the numerical, mean, median and standard deviation values for continuous variables. Categorical variables were described in percentage and proportion. The statistical analysis of data was performed using the Mann-Whitney U test. Regarding the association between categorical variables, Pearson's chi-square test and Fisher's exact test were performed. Statistical analyses were used the statistical program RStudio 2022.07.1 and Microsoft Excel 2016, adopting statistical significance of 5% ($p < 0.05$).

RESULTS

- **Sociodemographic data**

Fifty-one patients were enrolled, of these 39 were women (76.4%). Patient age varied between 18 and 72 years, with a mean of 43.3 years.

Education level of the sample was composed by complete higher education (19 - 37%), followed by complete high school (13 - 25%), incomplete higher education (7 - 14%), incomplete elementary (5 - 9.8%), complete elementary (4 - 7.8%), incomplete high school (2 - 3.9%) and illiterate (1 - 1.9%). Marital status was formed by married (22 - 43%), single (20 - 39%), stable union (5 - 9.8%), widowed (3 - 5.9%) and divorced (1 - 2%).

- **Vaccination status against COVID-19**

All 51 patients in the sample were vaccinated against COVID-19. Of these, 5 (9.8%) underwent only the initial regimen (2 doses) and 46 (90.1%) also underwent vaccination reinforcement, 27 (52.9%) underwent an initial regimen and only one booster and 19 (37.2%) underwent an initial regimen

and two boosters. In the initial regimen, the adsorbed COVID-19 inactivated vaccine (n = 8), BNT162 (n = 13) and ChAdOx1-S (n = 8), all in two doses, were applied. Boosters doses used were the adsorbed COVID-19 inactivated vaccine (n = 2), BNT162 (n = 47), ChAdOx1-S (n = 10) and Ad26.COV2.S (n = 6). The vaccines used in reinforcement differed from those used in the initial regimen in 40 of the 46 participants who underwent vaccine reinforcement with one or two doses.

Regarding the adverse effects of vaccination, 22 patients (43%) denied symptoms after any vaccine dose and 29 (57%) presented symptoms, most of which were mild and lasting less than 72 hours, characterized by local pain, asthenia, myalgia, headache and fever. The ChAdOx1-S vaccine was the one with the highest prevalence of side effects among those mentioned by the participants. Only 1 participant had a severe adverse effect characterized by anaphylactic reaction after application of the adsorbed COVID-19 inactivated vaccine. The adverse effects reported by vaccine are described in the Figure 1.

Of the patients listed, only 7 (14%) had COVID-19 after vaccination, all with mild disease. All these patients were using disease modifying drugs (DMD): 2 using interferon beta-1a, 2 using natalizumab, 2 using dimethyl fumarate and 1 using glatiramer.

- **Clinical characteristics of MS and relation to vaccination**

The relapsing-remitting MS type was present in 49 patients in the sample (96%) and secondary progressive MS in 2 (3.9%). No cases of the primary progressive form were seen in this study.

Several DMD were used, as shown in the Figure 2: glatiramer (n = 13 – 25%), dimethyl fumarate (n = 11 – 22%), natalizumab (n = 11 - 22%), interferon beta-1a (n = 7 – 13.7%), fingolimod (n = 3 - 5.9%) and ocrelizumab (n = 2 – 3.9%). Four patients (7.8%) do not use any DMD. Also, 34 patients (66.6%) already had undergone some other DMD and 17 (33.3%) were in use of the first DMD.

The disease time ranged from 0 to 26 years, with a mean of 8.1 years, median of 6.0 and standard deviation of 6.3.

Figure 1. Adverse effects reported by vaccine.

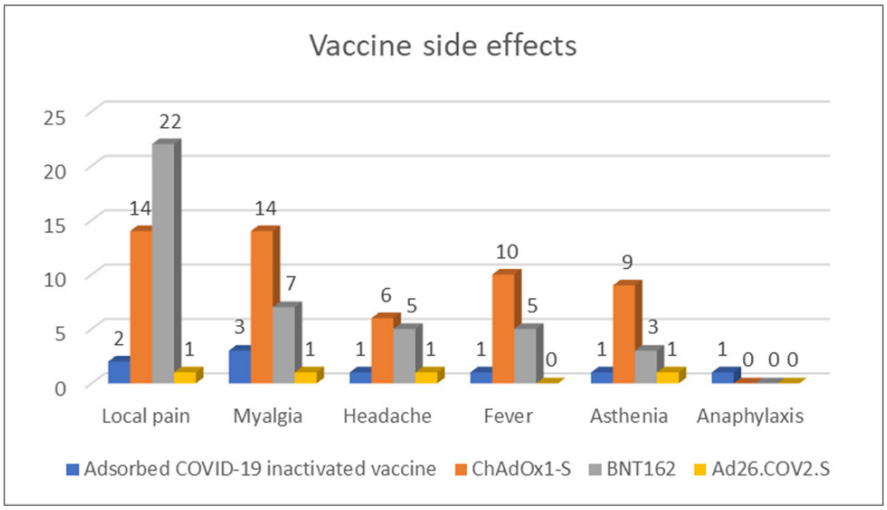
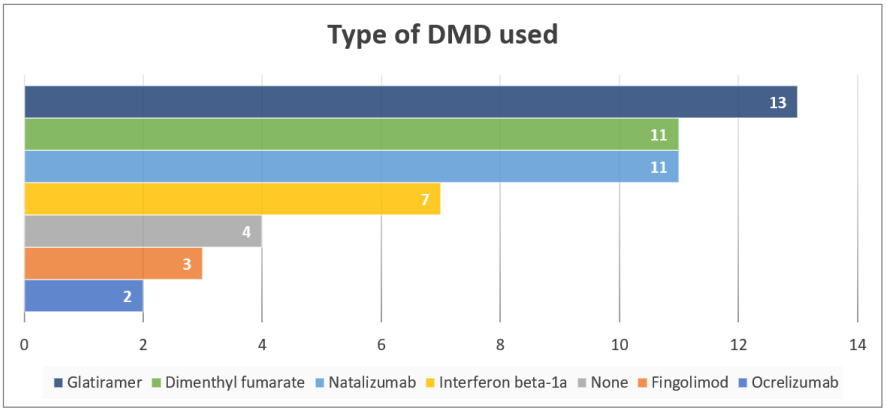


Figure 2. Type of DMD used in the patients.



The annualized relapse rate (ARR) was 0 in 34 individuals (67%), 0.5 in 11 (22%), 1 in 3 (5.9%) and 1.5 in 3 (5.9%). There was no significant increase in the ARR after administration of Adsorbed COVID-19 inactivated vaccine (p = 0.922), ChAdOx1-S (p = 0.417), BNT162 (p = 0.499) or Ad26.COV2.S (p > 0.999).

The mean current EDSS of the sample was 3.97, with a standard deviation 2.68. The EDSS before vaccination against COVID-19 and 6 months after remained unchanged in 45 individuals (88.2%). There was worsening in 6 (11.7%). Among patients who had worsening of the EDSS, 3 were without DMD use (50%). There was worsening of the EDSS in 3 patients after vaccination with BNT162, in 2 patients after adsorbed COVID-19 inactivated vaccine and in 1 patient after ChAdOx1-S, but all without statistical significance (p = 0.666, p = 0.284 and p = 0.577, respectively).

There was a clinical relapse within 6 months after vaccination against COVID-19 in 5 patients (9.8%), 2 (40%) of them were without DMD. There were no relapses within one month after vaccination. Regarding vaccines, 2 patients had relapses after vaccination with ChAdOx1-S (p > 0.999) and 3 after vaccination with BNT162 (p = 0.457). There were no relapses after vaccination with adsorbed COVID-19 inactivated vaccine or Ad26.COV2.S.

- **Psychological factors related to vaccination**

A total of 46 patients answered about psychological factors related to COVID-19 vaccination. Of these, 34 (74%) reported not having been afraid to get vaccinated and 12 (26%) had some fear. Of the patients who related fear, 9 related fear due to the fact of having an autoimmune disease and 4 related fear of having a new relapse of MS.

The main sources of fear were social networks (cited 5 times), television (cited 4 times), friends and family (cited 4 times), personal distrust (cited 2 times) and scientific articles (cited 1 time).

There was intentional delay at the beginning of vaccination in 5 (10.8%), with a mean delay of 4 months in these patients.

Among the motivations for vaccination, 52 responses were mentioned, in which 82.6% were not getting COVID-19, 7.6% not transmitting the virus, 5.7% obligation to perform social activities that required vaccination and 3.8% for medical guidance.

DISCUSSION

In this study, we analyzed data from patients with a previous diagnosis of MS according to the 2017 revised McDonald criteria[10] submitted to vaccination against COVID-19 in a tertiary center in northeastern Brazil, evaluating, in a real-life experience, the safety, side effects and psychological factors related to vaccination for this population.

Vaccination adverse effects were observed in 56.8% of the sample, being reported only 1 severe adverse event after adsorbed COVID-19 inactivated vaccine out of 108 adverse effects reported. Our sample is similar to other real-life studies in MS patients vaccinated against COVID-19, as well as similar to the incidence records of side effects in the general population.[11–13] In the literature, anaphylactic reactions were related after vaccination with BNT162 and Adsorbed COVID-19 inactivated vaccine.[14]

Myalgia was reported as the main adverse condition after vaccination with adsorbed COVID-19 inactivated vaccine. After ChAdOx1-S vaccine, local pain and myalgia were most common; After BNT162, local pain; Ad26.COV2.S had 4 adverse effects out of 6 received doses, including local pain, myalgia, headache and asthenia. These data are similar to those reported in the literature.[15,16] According to Yamout et al, vaccines against COVID-19 may be related to serious side effects, in which ChAdOx1-S and Ad26.COV2.S, both of viral vector technology, have a higher incidence of thrombotic events.[17] Some cases of Guillain-Barré syndrome were reported after vaccination with Ad26.OV2.S. There are reported cases of Bell's palsy after vaccination with BNT162, with good response to corticosteroid therapy.[18] Thrombotic complications, facial palsy and Guillain-Barré syndrome were not found in our sample.

Six patients in this study (11,7%) had worsening of EDSS within 6 months after vaccination, but 3 of them were not using any DMD, a factor that may contribute to the progression of MS.[19] In addition, there were 5 cases of relapses after immunization, but only 1 within the first month after the vaccine. This specific patient used a DMD (glatiramer) regularly and was administered BNT162. There are reports of MS relapses associated with hepatitis B vaccination,[20] but there is no robust scientific correlation of new MS relapses that occurs after vaccination having a direct causal relationship with some vaccine against COVID-19 so far.[15,21] It is important to highlight a 1 study by Ismail & Salama, that showed 102 cases of central nervous system demyelination after COVID-19 infection, in which only 32 were reported after vaccination, evidencing the higher risk of demyelination associated with SARS-CoV-2 infection than with immunization against it.[22,23]

Of the 5 patients who had relapses after the vaccine, only 2 evolved with worsening of the EDSS and these did not use DMD. This fact may be more related to an increased risk of relapse associated with the absence of treatment rather than to an effect of the vaccines.[19,23]

We also report 7 cases of COVID-19 after vaccination, all mild cases. Two patients received only the initial two doses and 5 had the initial doses with 1 or 2 boosters. The adsorbed COVID-19 inactivated vaccine, messenger RNA and viral vector technologies were used. These patients used DMDs, among them interferon beta-1a, glatiramer, dimethyl fumarate and

natalizumab. According to Ciotti et al., the use of DMDs, with the exception of interferon beta-1a, may cause some negative effects on the immunological response to SARS-CoV-2 vaccines, while still maintaining some protection.[24]

In Brazil, the National Plan for The Operationalization of Vaccination against COVID-19 was followed, accepting, as reinforcement, other vaccines than the one applied in the initial immunization. Vaccination against COVID-19 began worldwide on December 8, 2020, but the beginning in Brazil was only on January 17, 2021.[6] We found that, in addition to the delayed start of vaccination for the Brazilian population, there was still a voluntary delay in vaccination in 10.8% of the participants of our sample. Also, 26% of our sample claimed that they were afraid of COVID-19 vaccination. Part of this fear may have been due to the growing anti-vaccine campaign worldwide, causing doubts, vaccination delay and unscientific skepticism in the most diverse levels of education[25] and socioeconomic levels.[26]

Several studies have shown how content related to vaccination is displayed extensively on social networks, many times bringing false content to the population.[27] In the present study, social media was the main source of fear, being inferred as an important reason for the delay of vaccination in some of our patients. Future vaccination campaigns will have to take into account the power of vaccine-related misinformation when planning their strategies.

This study has limitations regarding a small sample and no longitudinal evaluation. We also had a highly heterogeneous sample, with many different vaccines combined in the analysis. In the psychological evaluation, we had 5 participants (9.8% of the total sample) who were not willing to participate.

Although a small unrandomized sample, this study demonstrates a real-life analysis of a tertiary center in Brazil, evaluating the influence of several vaccines in patients with MS. We assessed the effect of Adsorbed COVID-19 Inactivated Vaccine (Butantan®/Sinovac® and CoronaVac-Sinovac®), which had not been included in most previous studies in people living with MS, contributing with new data about the security of this vaccine. The analysis of psychological factors in this profile of Brazilian patients with MS is innovative, contributing to demonstrate the harm that anti-vaccine campaigns can cause in the population.

CONCLUSION

We have described sociodemographic and clinical characteristics of patients with MS vaccinated against COVID-19. Adverse events were common, but mostly mild. None of the patients had relapses in the first month after vaccination and the ARR did not change after vaccination. Few patients had relapses in the 6 months after vaccination or EDSS worsening, and most of these were not taking disease modifying drugs. This study adds new data to reinforce the safety of COVID-19 vaccines, including the Adsorbed COVID-19 Inactivated Vaccine (Butantan®/Sinovac® and CoronaVac-Sinovac®), in patients with MS. The fear of vaccinating led to delay in some patients, and social networks were the main source of fear.

AUTHOR CONTRIBUTIONS

Pedro Luiz Lopes participated in the acquisition and analysis of data, preparation of the draft and final writing.

Francisco Bruno Santana da Costa participated in the conception and initial design of the study.

Avelino Missialdes Dutra Júnior participated in data acquisition, reviewing, and critical analysis of the study.

Paulo Ribeiro Nóbrega participated in data acquisition, manuscript writing and reviewing, and critical analysis of the study.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

STATEMENTS

Patients from this research signed and agreed with a free and informed consent form for this study.

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How to cite:
Lopes PL, Costa FB, Braga P Neto, Sobreira MA Neto, Dutra AM Júnior, Nóbrega PR. Vaccination for COVID-19 in patients with multiple sclerosis: sociodemographic aspects, safety and associated psychological factors. 2024;64(1):e83250.