MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
SUMY STATE UNIVERSITY
MEDICAL INSTITUTE

Eastern Ukrainian Medical Journal

2, Rymskogo-Korsakova st., Sumy 40007, Ukraine
e-mail: EUMJ@med.sumdu.edu.ua
eumj.med.sumdu.edu.ua
ISSN: 2663-5909 (print)

ABSTRACT

DOI: https://doi.org/10.21272/eumj.2023;11(1):47-52

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DIFFERENTIAL DIAGNOSIS OF EXACERBATIONS AND PSEUDO-EXACERBATIONS AGAINST THE BACKGROUND OF SARS-COV-2 BY THE EXAMPLE OF A CLINICAL CASE OF A PATIENT WITH MULTIPLE SCLEROSIS

Abstract. Due to the COVID-19 pandemic, there is an increasing need for information on how SARS-CoV-2 affects individuals with multiple sclerosis (MS). The patients receiving disease-modifying therapy (DMT) for MS are more likely to require medical attention for infection than the general population. SARS-CoV-2 can cause the worsening of MS symptoms and be mistaken for a relapse, so physicians must carefully assess whether a patient is experiencing a relapse or pseudo-exacerbation. Thus, there is a necessity for science-based guidelines on how to lower the risk of infection, as well as an early differential diagnosis of relapse and pseudo-exacerbation, and effective care for MS patients with COVID-19.

Materials and methods of research: a patient with a history of MS treated with DMTs. The patient presented with worsening disease symptoms, likely exacerbation, and was diagnosed with COVID-19.

Results: a thorough analysis of existing literature was conducted, along with a quick examination of how DMT was used in MS patients with COVID-19. The patient we dealt with was receiving DMT and experienced a severe illness. Timely use of intravenous corticosteroids and antibiotics allowed taking under control the activity of the pathological process. Fortunately, the outcome was favorable.

Conclusions: this evaluation presents information about the clinical features, results, and functions of DMTs in MS patients infected with SARS-CoV-2. Healthcare professionals must carefully consider the possibility of relapse in MS patients with COVID-19, particularly during the pandemic, and should look out for pseudo-exacerbations. While many cases demonstrated a mild course of illness and successful recovery with DMTs, additional investigation is required to create guidelines supported by evidence.

Keywords: COVID-19, pseudo-exacerbation, Interferon beta-1b, multiple sclerosis, relapse, SARS-CoV-2, disease-modifying therapy.

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ДИФЕРЕНЦІАЛЬНА ДІАГНОСТИКА ЗАГОСТРЕННЯ ТА ПСЕВДОЗАГОСТРЕННЯ НА ФОНІ SARS-COV-2 НА ПРИКЛАДІ КЛІНІЧНОГО ВИПАДКУ ХВОРОГО ІЗ РОЗСІЯНИМ СКЛЕРОЗОМ

Через пандемію COVID-19 у світі постійно зростає потреба в інформації про вплив SARS-CoV-2 на осіб із розсіяним склерозом (РС). Хворі, які приймають хворобо-модифікуючу терапію (ХМТ), мають набагато більший ризик інфікування будь-яким інфекційним патогеном, ніж особи з загальної популяції. SARS-CoV-2 може спричиняти погіршення симптомів РС, яке помилково можна прийняти за справжнє загострення, що насправді буває не завжди. Тому лікарі повинні ретельно підходити до ранньої діагностики рецидивів та псевдозагострень, що може впливати на вибір тактики лікування. Таким чином, існує необхідність у науково обґрунтованих рекомендаціях щодо способів зниження ризику інфікування, ранньої диференціальної діагностики рецидивів і псевдозагострень, а також ефективного догляду за хворими на РС із COVID-19.

Матеріали та методи дослідження: в статті описуються особливості клінічного випадку хворого на РС, який перебував на ХМТ. Було виявлено загострення симптомів РС через COVID-19, яке розцінене як справжнє загострення.

Результати: було проведено ретельний аналіз існуючої світової літератури, а також короткий аналіз того, як ХМТ можливо використовувати у хворих на РС на фоні COVID-19. Описаний у статті клінічний випадок хворого з тяжким загостренням РС, яке було спровоковане SARS-CoV-2, показує, що в результаті проведення своєчасної інтенсивної патогенетичної терапії вдається стабілізувати стан хворого, а на кінець курсу лікування – навіть частково зменшити неврологічний дефіцит.

Висновки: медичні працівники повинні вміти проводити диференціальну діагностику між рецидивом та псевдозагостренням у хворих на РС, особливо в поєднанні з COVID-19. У той час як численні статистичні дані зі всього світу в багатьох випадках продемонстрували легкий перебіг захворювання та успішне одужання на фоні ХМТ, все ще залишається потреба у додаткових клінічних дослідженнях для створення клінічних настанов, які засновані на принципах сучасної доказової медицини.

Ключові слова: COVID-19, псевдозагострення, інтерферон бета-1b, розсіяний склероз, SARS-CoV-2, хворобо-модифікуюча терапія, загострення.

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How to cite / Як цитувати статтю: Lychko V, Kolenko O, Burtyka M**.** Differential diagnosis of exacerbations and pseudo-exacerbations against the background of SARS-COV-2 by the example of a clinical case of a patient with multiple sclerosis. *EUMJ*. 2023;11(1):47-52
DOI: https://doi.org/10.21272/eumj. 2023;11(1):47-52

INTRODUCTION / ВСТУП

Multiple sclerosis (MS) is an immune-mediated disorder of the nervous system and one of the most common causes of disability in the human population. The disease is provoked by hard demyelination and axonal degeneration leading to progressive damage of the nervous system and accumulation of persistent disability [1]. The autoimmune hypothesis involves the dysregulation of autoreactive T cells with B lymphocytes and macrophages, in which virus-induced immunopathology plays a relevant role [2].

Acute relapse (attack or flare-up) is the spontaneous onset of new or worsening of existing neurological symptoms, leading to an increase in the Expanded Disability Status Scale (EDSS) by at least 0.5 points and lasting more than 24 hours. It could be caused by systemic infection, especially upper respiratory tract infection or flu. The risk of relapse increased during a predefined at-risk period between 2 weeks before and up to nearly 2 months after the infection. Evidence of inflammatory activation was supported by high plasma and cerebrospinal fluid concentrations of soluble intracellular adhesion molecules and specific chemokines during infections and exacerbation [3].

It is crucial to understand that sometimes symptoms can occur without any new damage, and these flare-ups are known as pseudo-exacerbations. Pseudo-exacerbations are temporary worsening of symptoms that do not involve actual inflammation or damage to the myelin, but are triggered by other factors, such as other illnesses or infections, exercise, warm environment, depression, exhaustion, and stress. It's important to check for a fever when symptoms flare up since even a minor infection and a slight increase in temperature can lead to symptom appearance [4].

As a result of the use of disease-modifying therapy (DMT), a decrease in the frequency of exacerbations of MS has been noted [5]. Numerous clinical studies have shown that early onset and long-term use of DMT reduce the frequency and severity of relapses and delay the development of disability. However, even adequate DMT does not guarantee 100% prevention of exacerbations; relapses continue to occur, leading to a temporary or permanent disability of patients [6]. Therefore, the correct recognition of relapses vs. pseudo-exacerbations is a key to effective management in urgent modern neurology.

Patients receiving DMT for MS have a higher background risk of infection-related healthcare utilization when compared to the general population. There are indications that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can trigger new onset or relapses of the neuro-immunological disease like MS. The article reports a patient with relapsing-remitting multiple sclerosis (RRMS) under DMT who experienced a relapse of RRMS after COVID-19.

Materials and methods of research. Describes a person who has MS and is taking DMT. The patient was found to have exacerbated MS symptoms due to COVID-19, likely a relapse. The systematic online search of articles utilizing the search terms ”Coronavirus, SARS-COV-2 and Multiple sclerosis”, published between January 2020 and October 2023, was performed.

Case presentation. A 53-year-old man with a history of RRMS for eight years, controlled by Interferon beta-1b for three years, was presented to the emergency department of the Sumy Clinical Hospital #4 with generalized weakness and shortness of breath.

His medical history included hypertension with no other significant anamnestic data. Considering the MS, the patient was on Methylprednisolone before Interferon beta-1b. The last two extensive relapses were dated to 2014 and 2015. In 2014, the patient had an episode of light double-side optic neuritis; in 2015, he presented with lower extremity weakness. MRI brain from 2018 showed stable demyelinating plaques with no abnormal enhancing lesion. His EDSS was estimated to be 4.5 for his current episode, and his baseline EDSS was 3.0. He could perform his routine activities independently and did not require ambulatory aid.

In November 2020, the patient's mother developed COVID-19. After one week, the patient started complaining of anosmia, fever, and headache, followed a few days later by hand paresthesia, asymmetry of the face and muscle fatigue. A general practitioner attributed it to COVID-19.

On examination, he was febrile, desaturating with pulse oximetry 86%, and required 2 L oxygen through the nasal cannula. Complete blood count showed slight increase leukocyte and lymphocyte count, CD^{4+}

and CD^{8+} counts were within the normal range (964 cells/uL and 506 cells/uL), and the immunoglobulin subtypes (including IgG, IgM and IgA) were usual. C-reactive protein was elevated to 63 mg/L, ferritin levels – to 588 ng/mL, aspartate aminotransferase – to 610 U/L, alanine aminotransferase was normal, blood urea nitrogen was elevated to 28 mg/dL, and creatinine was 1.91 mg/dL.

The neurological examination showed high tendon reflexes at four limbs and a central involvement of the seventh left cranial nerve. Cerebral MRI revealed bilateral non-enhancing white matter perivenular lesions with blurred edges involving the periventricular, and subcortical areas, as well as the brain stem.

Chest X-ray showed the double side lower lobe infiltrates. CT chest showed patchy ground glass infiltrates at the lung bases bilaterally. The nasopharyngeal reverse transcription polymerase chain reaction for SARS-CoV-2 was positive. He was admitted as a patient of severe COVID-19, according to the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) severity index guidelines [7].

The patient was started on azithromycin and intravenous steroids for seven days. His symptoms improved after three days of treatment, partially recovering the sensory symptoms and facial palsy. No additional oxygen supplementation was required. He likely had an exacerbation of MS from an ongoing COVID-19 infection. His clinical course of COVID-19 lasted approximately three weeks, after which he tested negative. He was discharged after 22 days of admission once he returned to baseline. His EDSS at discharge was 5.0, which was a little higher than his baseline. The patient continued on Interferon beta-1b following discharge.

Discussion. The negative tendency for combination cases of MS and COVID-19 have been emerging during last few years. It is already known that MS patients are at a higher risk for infections than the general population. A few multi-database studies conducted to assess the risk of COVID-19 in MS patients reported higher infection rates in the group with MS compared to the non-MS group [8, 9].

The coronavirus pandemic led to pertinent questions regarding the course and outcome of COVID-19 in patients with MS, specifically those on DMT. Most of the patients (nearly 96%) had a mild COVID-19 disease, with only 4% suffering from a severe infection in a large multicenter Italian study that evaluated 232 MS patients with confirmed SARS-CoV-2 infection. 222 (96%) patients recovered from the disease. Of 10 severe cases, 5 (2%) were fatal. It confirms that the outcomes of COVID-19 infections in MS patients are similar to the general population. In the described case, the patient had a severe course of COVID-19 with partial recovery after pathogenic treatment. DMT course was continued after 4-6 weeks of recovery from COVID-19 infection [10].

A clinical case of SARS-CoV-2 infection in an MS patient with ocrelizumab was described. A possible protective role of immunosuppressive therapy for COVID-19 infection was also explored. The patient had a depleted B-cell reserve and low levels of proinflammatory cytokine detection during the infection leading to a mild clinical course [11].

For everyday practice, it is also important to recognize the manifestation of COVID-19 in patients with MS. Our case represents a patient with MS on DMT, who presented with worsening MS symptoms and complained of weakness, fatigue, shortness of breath, likely a relapse due to COVID-19. The severity index in the patient was severe according to the ATS/IDSA severity criteria [7].

Glatiramer acetate is an immunomodulatory agent that does not cause T-cell depletion but rather induces CD^{8} T-cell response in patients with MS [12]. Dimethyl fumarate provokes a reduction in circulating memory B-cells as well as in T-helper cells (CD^{4}) and cytotoxic T-cells (CD^{8}), activates nuclear-related factor 2 involved in antioxidative response pathways leading to additional cytoprotective effects [13]. Ocrelizumab is anti-CD-20 monoclonal antibody therapy in RRMS. It affects B-cell lineage and is not associated with severe viral infections [14]. All these medicines are considered to be very low risk, low risk and intermediate risk categories of disease-modifying agents, respectively, to attribute to the risk of novel coronavirus infection [15, 16]. If the antiviral response to SARS-CoV-2 is driven mainly by CD^{8+} cytotoxic T-cells or natural killer cells, we should be informed of the risk associated with different classes of DMT in case a patient with MS develops COVID-19.

Our patient recovered from the novel coronavirus infection and continued on disease-modifying therapy. We were worried about the continuation of DMT in the MS patient, which induces an immunosuppressed state and predisposes to infections. Some authors have recommended decreasing the dose of DMT in MS patients during the pandemic period to reduce the risk of contracting the disease. Aging may lead to increased terminally differentiated late effector memory T cells. Still, DMT reduces the number and functionality of the

lymphocytes, which can predispose to the higher risk of progressive multifocal leukoencephalopathy secondary to lymphopenia in this group of patients [17].

T-cells that lack interleukin-2 are at a disadvantage in terms of effector cell differentiation and have a higher threshold for productive T-cell receptor signaling, which results in less activation and hinders viral clearance. In older patients, DMTs may exacerbate this issue, leaving them vulnerable to chronic infections [18]. The loss of CD^{28} in auto-immune diseases indicates premature aging of the immune system, which can lead to reduced T-cell priming and activation by antigen-presenting cells (APCs). Research has revealed impaired dendritic cells maturation, which lowers the capacity for antigen uptake and presentation. Moreover, the loss of costimulatory signals with APCs may also contribute to impaired T-cell activation in the aging process. As a result, DMTs may hinder APC function and have implications for immunosurveillance, regardless of T-cell numbers [19].

It is recommended that MS patients who develop severe COVID-19 should temporarily stop taking DMT for at least four weeks. Further research is necessary to determine the continuation of disease-modifying therapies in patients with both MS and COVID-19 symptoms requiring investigation. MS patients can experience worsening symptoms due to COVID-19, which may appear as a pseudo-exacerbation [16]. Physicians should be cautious and consider the possibility of a pseudo-relapse when treating MS patients during the COVID-19 pandemic. The use of intravenous steroids for pseudo-exacerbation in MS patients is not recommended. The effectiveness of methylprednisolone in patients with COVID-19 respiratory distress is being investigated. Most MS patients with mild COVID-19 can continue immunotherapy, but for those with moderate to severe symptoms, the continuation of treatment is still uncertain.

CONCLUSIONS / ВИСНОВКИ

It is uncertain whether DMT is a risk factor for COVID-19 in MS patients, and more research is needed to establish guidelines for managing these patients. While most MS patients have mild cases of COVID-19, a small number of experience severe symptoms and some have died. Various factors such as age, weight, underlying medical conditions, and ambulatory status can contribute to the severity of COVID-19 in MS patients.

COVID-19 can cause MS symptoms to worsen and be mistaken for a relapse, so physicians must carefully assess whether a patient is experiencing a relapse or pseudo-exacerbation.

Physicians face difficulty deciding whether to continue immunotherapies or DMT for MS patients, as some DMT may increase infection risks. Further studies and data are necessary to establish standardized guidelines for caring for MS and other immune-mediated disorders.

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

FUNDING / ДЖЕРЕЛА ФІНАНСУВАННЯ

None.

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

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Received 20.02.2023
Accepted 15.03.2023

Одержано 20.02.2023
Затверджено до друку 15.03.2023

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