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ORIGINAL ARTICLE

Chronic infection and malignancy screening in Mexican patients with multiple sclerosis

Lizeth Zertuche-Ortuño, Linda Rivera-Sarabia, Juan J. García-Ramírez, Víctor Hernández-Castillo, and Irene Treviño-Frenk*

Department of Neurology, Multiple Sclerosis Clinic, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Mexico City, Mexico

Abstract

Objective: *Screening studies are recommended to rule out neoplasms and chronic infections before starting disease-modifying therapies (DMTs). To illustrate the importance of screening before DMT initiation and to show, the most frequent findings in patients with multiple sclerosis (MS) in a developing country.* **Methods:** *We analyzed patients admitted to the MS clinic from 2020 to 2023 who underwent screening before the initiation of DMT. All patients were sampled for: quantiFERON for tuberculosis (TB), varicella zoster immunoglobulin G levels, human immunodeficiency virus, Hepatitis B, Hepatitis C virus, venereal disease research laboratory, papanicolaou smear, and mammogram in women over 40.* **Results:** *We analyzed 103 patients, 74 of whom were women (71.8%), with a mean age of 42.8 ± 15. Pathological findings were detected in 21 (20%) patients: latent TB in 12 (11.6%), cervical human papillomavirus infection in 3 (2.9%), benign thyroid nodule in 2 (1.9%), liver TB in 1 (0.9%), penile squamous carcinoma in 1 (0.9%), thyroid carcinoma in 1 (0.9%), and breast papilloma in 1 (0.9%). Patients who received DMT did not develop any complications.* **Conclusions:** *The pathological findings did not influence the final treatment decision. However, screening tests are essential for the early detection and management of chronic conditions. Conducting these tests before initiating DMTs helps identify potential co-morbidities or contraindications to immunosuppressive treatments, ensuring safer and more effective patient care.*

Keywords: *Chronic infections. Multiple sclerosis. Prevention. Screening. Treatment initiation.*

Tamizaje de infecciones crónicas y malignidad en pacientes mexicanos con esclerosis múltiple

Resumen

Objetivo*: Los estudios de cribado se recomiendan para descartar neoplasias e infecciones crónicas antes de las terapias modificadoras de la enfermedad. (TME). Ilustrar la importancia del cribado previo al inicio de TME, mostrar los hallazgos más frecuentes en pacientes con esclerosis multiple (EM) en un país en vías de desarrollo.* **Métodos***: Se analizaron los pacientes ingresados en la consulta de EM entre 2020-2023, a quienes se les realizó un perfilamiento previo al inicio de TME. A todos los pacientes se les tomaron muestras de: quantiFERON para tuberculosis, niveles de IgG varicela zoster, virus de la inmunodeficiencia humana, hepatitis B, hepatitis C, VDRL, citología vaginal y mamografía en mujeres mayores de 40 años.* **Resultados***: Se analizaron 103 pacientes, de los cuales 74 eran mujeres (71.8%), la edad media fue de 42.8 ± 15 años. Se detectaron hallazgos patológicos en 21 (20%) pacientes: tuberculosis latente 12 (11.6%), infección cervical por VPH 3 (2.9%), nódulo tiroideo benigno 2 (1.9%), tuberculosis hepática 1 (0.9%), carcinoma escamoso de pene 1 (0.9%), carcinoma de tiroides 1 (0.9%) y papiloma*

***Correspondence:**
Lizeth Zertuche-Ortuño
E-mail: Lizeth.zert@gmail.com

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de mama 1 (0.9%). Los pacientes que recibieron TME no desarrollaron ninguna complicación. **Conclusiones***: Los hallazgos patológicos no influyeron en la decisión final del tratamiento. Sin embargo, el perfilamiento es esencial para la detección temprana y el tratamiento de enfermedades crónicas. La realización de estas pruebas ayuda a identificar posibles comorbilidades o contraindicaciones para los tratamientos inmunosupresores, lo que garantiza una atención al paciente más segura y eficaz.*

Palabras clave: *Esclerosis múltiple. Tamizaje. Infecciones crónicas. Prevención. Inicio del tratamiento.*

Introduction

Multiple sclerosis (MS) is a chronic, demyelinating, and neurodegenerative disease of the central nervous system. It is the leading cause of non-traumatic disability among young adults, affecting 2.3 million people worldwide[1].

The growing number of approved disease-modifying therapies (DMTs) increases the possibility of adapting treatment plans to individual patient needs, in terms of efficacy, safety issues, and preferences[2]. Current trends toward initiating high-efficacy DMTs have gained ground due to accumulating evidence supporting their efficacy in slowing disease progression and reducing clinical disability[3].

Depending on their mechanisms of action, immunomodulatory and immunosuppressive DMTs increase the risk of infections, including reactivation of latent pathogens, as well as asymptomatic chronic or new infections[4].

People living with MS are a risk group for chronic infections, with studies reporting hazard ratios between 2.5 and 3.5 times higher for MS patients compared with controls[5]. People with MS also experience a reduced life expectancy of up to 7-14 years compared to the general population[6,7].

While these therapies claim an acceptable safety profile, they exert a considerable immunosuppressive effect, potentially heightening the theoretical risk of infections and malignancies. Given these considerations, it is advisable to conduct screening studies before starting DMTs to identify and exclude any neoplasms or chronic infections that might pose contraindications to their use[8].

The Delphi consensus statement provides a comprehensive list of screening studies recommended for baseline infectious disease evaluation before initiating any DMT[9]:

- Serologic assessment: Toxoplasma immunoglobulin G (IgG), Hepatitis B core antibody (HBcAb), surface antigen (HBsAg), surface antibody (HBsAb), Hepatitis C virus antibody (HCVAb), human immunodeficiency virus (HIV), venereal disease research laboratory (VDRL)
- Immunoglobulins for varicella-zoster virus (VZV IgG), cytomegalovirus (CMV IgG), Epstein-Barr virus (EBV IgG), measles IgG, and rubella IgG
- Papanicolaou (Pap) smear with human papillomavirus (HPV) test
- Tuberculosis (TB) testing: Interferon-γ release assay (IGRA) or purified protein derivative intradermal (PPD- intradermal reaction) test.

Methods

An observational retrospective study was performed, with the approval of the Ethics Committee of our institution. We analyzed patients admitted to the MS Clinic of the Instituto Nacional de Ciencias Médicas y Nutrición “Salvador Zubirán” in Mexico City, from January 2020 to December 2022, who underwent screening before the initiation of DMT.

We based our profiling on the recommendations of the Delphi consensus, adapting them to suit our population. Patients were sampled for IGRA with QuantiFERON®-TB Gold for TB, VZV IgG, HIV, HBcAb, HBsAg, HBsAb, HCVAb, and VDRL. Women underwent a Pap smear with a cervical HPV test, and those over 40 years of age also had a mammogram.

Toxoplasma IgG, CMV IgG, EBV IgG, Measles IgG, and Rubella IgG tests were not included, as they are not routinely recommended before starting DMTs.

In the applicable cases, thoracic radiography, thyroid function tests, and thyroid ultrasound were performed. Fourteen patients who were not completely evaluated and lost to follow-up were excluded.

The rest of the demographic variables, clinical characteristics, pharmacological treatment, and comorbidities were obtained from medical records. Patient data were collected and captured in a database in the Statistical Package for the Social Science V25 program for analysis. Descriptive analysis of nominal variables was performed using percentages and proportions, and for numeric variables, mean and standard deviation were used. Bivariate analysis was performed with numeric variables using the Student’s t-test.

Results

We analyzed 103 patients, 74 were women (71.8%), and the average age was 42.8 ± 15, the mean time living with MS was 12.75 years, average expanded disability status scale score was 2.72 ± 1.8. Sixty-six patients (65%) presented with relapsing-remitting MS, 26% with secondary progressive MS, and 9% with primary progressive MS.

Previous comorbidities were found in 26 patients (25%) patients, which were: hypothyroidism 9 (8%), diabetes mellitus type 2 6 (5%), hypertension 3 (2%), lupus 3 (2%), inflammatory colitis 1 (0.9%), neurofibromatosis 1 (0.9%), uveitis 1 (0.9%), Type 1 diabetes mellitus (0.9%), and ischemic stroke 1 (0.9%).

Pathological findings were detected in 21 (20%) patients, as seen in table 1. In our series, we identified three cases of cervical HPV infection which resolved with electrofulguration. A patient with a verrucous dermal lesion on the penis was found to have a low-grade HPV+ neoplasia, which was resolved with excisional biopsy. No other male patient reported genital lesions, so no further screening tests were performed. None of our patients with latent TB (LTB) exhibited any pathological findings on chest tomography indicative of active TB. All individuals received prophylactic treatment in collaboration with infectious disease specialists, and no complications arose at the beginning of the DMT.

An extra-pulmonary manifestation of TB was observed in only one patient, a 35-year-old woman, previously treated with alemtuzumab in 2016, who underwent screening tests in 2023 following a clinical relapse. She presented persistent elevation of liver function tests, with a liver biopsy revealing granulomatous inflammation and a positive *Mycobacterium tuberculosis* polymerase chain reaction. At present, she is under surveillance and has not initiated DMT yet.

Patients with other pathological findings were effectively treated and subsequently administered DMT, as described in table 1. As of now, they have not experienced any complications.

The interval between screening tests and the initiation of DMT was 21.3 ± 14 days for patients without pathological findings. In contrast, for patients with pathological findings, this interval increased significantly to 96.2 ± 78 days. This delay was statistically significant (p = 0.001), likely due to the need for additional tests and evaluations by other specialties.

Discussion

Our study results align with those documented in other international series, underscoring the significance of conducting profiling studies prior to starting a DMT. In accordance with Global Consensus Standards, clinicians are advised to evaluate DMT eligibility within 6 weeks of diagnosis[10].

We perform the same screening tests for all patients, regardless of the intended DMT. This standardized approach simplifies the process and helps prevent delays if a treatment change becomes necessary later. Although we recognize that this may not be applicable to all centers, we consider it a good clinical practice for efficient patient management.

At our center, we were able to initiate DMT within 3 weeks of diagnosis for patients without abnormalities in their screening tests. In contrast, this period extended to 3 months for patients with pathological findings. Our MS clinic is part of a tertiary care hospital, ensuring access to all necessary specialties for comprehensive case management. However, it is important to emphasize that healthcare in Mexico is highly variable, and the time required to initiate DMT is likely even longer in many other settings.

TB

The global prevalence of LTB stood at 24.8% as determined by IGRA, and 21.2% when using a 10 mm PPD cut-off[11]. In a major MS center in the United States, fewer than 10% of patients exhibited abnormal IGRA results: 2.0% tested positive, while 6.1% yielded indeterminate results[12]. In Mexico, there are an estimated 23,000-37,000 new cases of TB reported annually, resulting in a rate of 23 cases/100,000 inhabitants[13]. We observed an incidence of LTB of 11.9%, consistent with rates reported by other centers in Mexico[14]. The PPD or tuberculin test is recommended as the first choice for diagnosing LTB due to its cost-effectiveness. This test has a sensitivity of 75% for detecting *M. tuberculosis* infection in patients who are not vaccinated with Bacillus Calmette-Guérin (BCG) and 59% in those who are vaccinated. IGRAs have better specificity than the tuberculin test and are not affected by BCG vaccination under normal conditions[15].

LTB linked with immunosuppressive risk factors poses a yearly risk of active TB ranging from 5% to 10%[16].

LTB screening is suggested for patients with MS who will be started on teriflunomide, fingolimod, natalizumab, alemtuzumab, rituximab, ocrelizumab or dimethyl fumarate (DMF). The use of alemtuzumab, cladribine, and teriflunomide is correlated with a slightly elevated risk of active TB compared with the general population, particularly in areas endemic to TB[17].

Table 1. Pathological findings in MS patients, treatment strategies, and the selection of DMTs post-screening

Pathological finding	Patients, n (%) (n = 103) (%)	Treatment	DMT chosen after screening
Latent tuberculosis	12 (11.6)	Rifampicine or isoniazide for 6 months	Cladribine Ocrelizumab Fingolimod
Pap smear with atypical HPV+cells	3 (2.9)	Electrofulguration	Cladribine Ocrelizumab
Benign thyroid nodule	2 (1.9)	Surveillance	Siponimod Cladribine
Liver tuberculosis	1 (0.98)	Six-month RIPE TB treatment (rifampicine, isoniazid, pyrazinamide, ethambutol)	In surveillance
Low-grade neoplasia in penis HPV+	1 (0.98)	Excisional biopsy	Ocrelizumab
Papillary thyroid cancer	1 (0.98)	Thyroidectomy with radioiodine	Cladribine
Intraductal breast carcinoma	1 (0.98)	Excisional biopsy	Dimethyl fumarate

MS: multiple sclerosis; DMT: disease-modifying therapies; HPV: human papillomavirus; RIPE TB: tuberculosis.

However, there is no evidence of an elevated risk of active TB associated with interferons, glatiramer acetate, DMF, fingolimod, natalizumab, and anti-CD20 monoclonal antibodies[18].

Patients with Grade 3 or worse lymphopenia, recent methylprednisolone use, and those using fingolimod or DMF are at a significantly higher risk of having indeterminate IGRA test. Clinicians should be mindful of these factors, as adequate screening for LTB is crucial for safety with certain DMTs[19].

According to international recommendations, patients with MS who test positive for LTB should have a chest X-ray and TB preventive therapy with isoniazide or rifampicine should be considered, regardless of the treatment chosen[19].

The timing for starting a DMT depends on the urgency of disease control. Typically, DMT initiation is delayed for four to 8 weeks after starting LTB prophylaxis, mainly due to the potential risk of hepatotoxicity when both treatments are started concurrently. Therefore, periodic monitoring of clinical status and liver function is necessary[20].

In our study, all patients received preventive treatment without any complications or elevations in liver enzyme levels, enabling them to begin DMT 4 weeks after starting prophylaxis.

In MS patients who develop active TB, it is essential to promptly initiate a full course of anti-TB therapy. MS treatment should be paused until the intensive phase of treatment is completed. The decision to restart DMT should be made in collaboration with an infectious disease specialist[21].

Viral hepatitis

No cases of viral hepatitis were identified within our series. Clinical trials for MS typically exclude patients with evidence of HBV or HCV infection, consequently, determining the risk of hepatitis reactivation is challenging. This risk is relatively elevated in patients receiving B-cell-depleting agents or alemtuzumab[22].

Other risk factors for HBV infection include unvaccinated patients and profound lymphocytopenia. The risks of HBV activation in patients treated with fingolimod, DMF, and teriflunomide have not been well established but are likely low[23].

Considering the risk of HBV flares or reactivation among patients receiving immunosuppressant agents, it is recommended that all patients undergo screening for HBV infection. If HBcAb and HBsAb are negative, Hepatitis B vaccine (three doses) should be administered[24].

We recommend Hepatitis B vaccination for all patients with negative HBsAb serology. The recombinant Hepatitis B vaccine has an established safety profile, and current evidence indicates that it does not contribute to the development or reactivation of MS. Therefore, its administration can be safely considered whenever clinically indicated[25].

For patients planning to initiate anti-CD20 therapies (e.g., ocrelizumab, rituximab), evidence supports the effectiveness of administering the Hepatitis B vaccine at least 1 month before treatment initiation. In such cases, using an accelerated vaccination schedule has been shown to enhance the production of antibody titers[26,27].

Malignancy

In our study, we identified three malignancies: papillary thyroid carcinoma, intraductal breast papilloma, and penile carcinoma. All were detected in their early stages, and effective control was achieved, allowing all patients to subsequently initiate DMT. Importantly, none of these patients have experienced any complications following the initiation of immunosuppression. In a Danish population-based study, no increased incidence of malignancy was observed in patients with MS compared to the general population[28]. In addition, in another case–control study, the probability of developing cancer was 0.8 in the MS group, which did not show a significant difference from healthy subjects[29]. However, some studies have reported an increase in malignancy, particularly for the brain and urinary tract. This bias may be attributed to the periodic evaluation of patients by brain magnetic resonance imaging and urological assessment[30,31].

Sexually transmitted diseases (STDs)

Few studies have been conducted on sexual risk behaviors or STDs in patients with MS. It seems that individuals living with MS are at similar risk as the general population. No significant difference was found in sexual debut, number of partners, or risk behaviors for STDs[32].

In our series, we identified three cases of cervical HPV infection which resolved with electrofulguration. A patient with a verrucous dermal lesion on the penis was found to have a low-grade HPV + neoplasia, which was resolved with excisional biopsy. No other male patient reported genital lesions, so no further screening tests were performed.

The primary HPV-related concern is cervical cancer, with 96% of cases attributed to HPV infections[33]. Cell-mediated immunosuppression is indeed a risk factor for preneoplastic and neoplastic HPV-related diseases. Several cases of cervical dysplasia have been reported with alemtuzumab, fingolimod, and natalizumab[34].

VZV

The presence of anti-VZV antibodies is approximately 92-95% in both MS patients and controls[35]. The risk of reactivation of latent herpesvirus infection is indeed heightened by immunosuppressive therapy, especially treatments that affect cellular immunity. Monitoring of VZV IgG levels is recommended, and vaccination is necessary before initiating DMTs for patients who test negative for antibodies[36].

Immune reconstitution therapies such as alemtuzumab or cladribine are associated with a higher risk of VZV reactivation. Prophylaxis with acyclovir is recommended during the 1st month of treatment with alemtuzumab and in cases of grade 3 lymphopenia with cladribine[37].

Ocrelizumab and fingolimod have been linked to an elevated risk of herpes virus infections, although usually presenting as mild cases. Routine antiviral prophylaxis is generally not necessary[38,39].

Other MS treatments, such as teriflunomide and DMF, do not appear to be clearly associated with an increased risk of frequency or severity of herpesvirus infections, although there are scattered case reports[40].

The main limitations of this study include its single-center design and its setting in a referral hospital specializing in internal medicine. This context may lead to a higher prevalence of comorbidities compared to the general population or patients treated at other neurological centers.

Conclusion

The implementation of screening tests before initiating DMTs facilitates the identification of potential comorbidities or contraindications to immunosuppressive treatments. Although our study did not observe any complications when starting DMTs, screening tests play a crucial role in detecting and managing chronic conditions early, which might otherwise remain undiagnosed until symptoms develop.

In Mexico and other developing countries, neurologists often act as the primary point of contact for managing patients with MS. This role encompasses the responsibility of addressing all relevant clinical factors and conducting comprehensive screenings. Access to other medical specialties and a collaborative approach to managing comorbidities are critical components of effective MS patient care.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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