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Original Article

Genitourinary Infectious Complications in Patients with Multiple Sclerosis and their Association with Disease Modifying Therapies

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HIGHLIGHTS

- Urinary tract infection (UTI) and Vaginitis are common infections among patients with multiple sclerosis (MS) and may be associated with increased morbidity and mortality.
- Disease Modifying Therapies (DMTs) as immunomodulators or immunosuppressive drugs increase the risk of urological infections.
- Since the urological infections in patients with multiple sclerosis (pwMS) can cause disease progression or relapse, they should be considered during the DMTs consumption.

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ABSTRACT

Introduction

Genitourinary Infections are common urological conditions societies have dealt with for decades. UTIs can have certain predisposing factors. Multiple sclerosis (MS) and Disease-Modifying Therapies (DMTs), primary MS treatment regimens demonstrate the effects of MS and DMTs on urological complications.

Methods

This paper is a cohort study conducted from June 2020 to October 2021 using prospectively collected data from every patient registered at Tehran's Multiple Sclerosis Referral Research Center. This study's inclusion criteria consisted of patients diagnosed with MS based on McDonald criteria and exposed to DMTs for at least six months. The exclusion criteria were being under 18 years of age, diagnosis change during the study, and mortality.

Results

We inducted a total of 905 patients into this study. We attempted 1:6 nearest neighbor propensity score matching without replacement with a propensity score estimated using logistic regression of the group on age and sex. 41 cases and 96 controls were discarded due to missing values for age and sex. Following matching, 11 more participants from the control group were discarded. Finally, data from 798 cases and 4788 control participants were analyzed. Urinary tract infection rate increased when patients were exposed to Rituximab, Beta1b, Fingolimod, Glatiramer, Azathioprine (P-value<0.05). Vaginitis incidence was increased when patients were exposed to Fingolimod and Glatiramer Acetate (P-value<0.05). EDSS and MS duration affected the UTI risk (P-value<0.05).

Conclusions

MS and the use of DMTs can result in an increased rate of urological infections. Healthcare workers should screen the MS Patients for UTI and vaginitis more often to prevent disease progression or choose the proper treatment regimen.

Keywords: Infections; Urology; Disease Modifying Therapies; Multiple Sclerosis; Risk Assessment

Introduction

Urinary tract infection (UTI) is common urological condition societies have dealt with for decades. UTI has certain risk factors that exacerbate UTI incidence in patients (1, 2). One of these conditions is multiple sclerosis (MS) (3). MS is a chronic neurological autoimmune disease caused by neuron demyelination in the brain, spinal cord, and nervous complex controlling the bladder (4, 5). These disabilities can be quantifiably described by Expanded Disability Status Scale (EDSS) (6). Also, MS has different subtypes based on the progression of the disease. They are relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS) (7). Therefore, a better understanding of MS can lead to better anticipation of its complication. MS can influence the risk of UTI and its MS treatment regimen (8, 9). Disease-Modifying Therapies (DMTs) are central to the MS treatment regimen (10). These drugs include Interferon Beta, Glatimer Acetat, Fingolimod, Natalizumab, Teriflunomide, Dimethyl Fumarate, Rituximab, Mycophenolate Mofetil, Azathioprine, Cyclophosphamide and Ocrelizumab (11-13). Rituximab and Fingolimod are the most acknowledged DMTs that correlate with UTIs (14, 15). Furthermore, Natalizumab is known for bacterial or fungal vaginitis, another type of urological complication (16). However, combining DMTs and MS may increase the risk of different urological side effects compared to other MS treatments (5).

In previous studies, a limited number of DMTs were examined for general infections rather than the exact type of infection and related exposure to DMTs in patients with MS (PwMS). Moreover, these studies did not specify the relation between EDSS, MS subtypes, and individual infections (17, 18). As a result, this study was conducted to demonstrate the urologic infectious complications associated with DMTs used in PwMS registered at the MS Referral Research Center of Tehran.

Methods

This paper is a cohort study conducted from June 2020 to October 2021 using prospectively collected data from every patient registered at Tehran's Multiple Sclerosis Referral Research Center. This study was approved by the Tehran University of Medical Sciences ethics committee (code: IR.TUMS.NI.REC.1400.003). This study's inclusion criteria consisted of patients diagnosed with MS based on McDonald criteria and exposed to DMTs for at least six months. The exclusion criteria were under 18 years of age, diagnosis change during the study, and mortality. We registered the demographic data, PwMS's subtype of MS, PwMS's duration of MS, past drug history, past medical history, the duration of each DMTs that patients had already used (the number of months each DMT was used), and EDSS from all patients at the beginning of the study. The patients were asked to visit the Multiple Sclerosis Referral Research Center of Tehran at least every six months for the duration of the study. If the patients could not make appointments, our researchers would contact them via phone. Any changes to EDSS of DMT of the patient were recorded during their appointment. All the medical records of any infection that occurred during the study were gathered and conducted for the study. The patient's infection claim without documentation was not considered a medical record. We acquired the patient's informed consent before obtaining any data at the beginning of this study. The data was imported to and analyzed by SPSS 24.

Results

We inducted a total of 905 patients into this study. We used propensity score matching to estimate the average marginal effect of the participant group for age and sex. We attempted 1:6 nearest neighbor propensity score matching without replacement with a propensity score estimated using logistic regression of the group on age and sex. This matching yielded adequate balance. The propensity score was estimated using a logistic regression of the group on age and sex. After matching, all standardized mean differences for the covariates were below 0.05, indicating adequate balance. Forty-one cases and 96 controls were discarded due to missing values for age and sex. Following matching, 11 more participants from the control group were discarded. Finally, data from 798 cases and 4788 control participants were analyzed. The demographic data are shown in Table 1. Data analysis of UTI and vaginitis are found in Table 2. There was a significant discrepancy among patients with higher EDSS in UTI occurrence (P-value<0.001, $\beta 0$=-10.263, $\beta 1$=4.146. UTI risk of occurrence was higher in patients with MS for a longer duration (P- value<0.001, $\beta 0$=-11.847, $\beta 1$=5.863). There was no meaningful difference between the subtypes of ms regarding the urologic complications (Table 3).

Discussion

Based on this prospective cohort study, MS and DMTs significantly increased the risk of UTI and bacterial or fungal vaginitis. Also, the duration of use of some DMTS could affect these infections. Therefore, this study

Table 1. Characteristics of the urological infectious complication study population

		Case	Control
Sex	**Male**	167	1005
	Female	631	3783
Patients Age	**Min**	18	18
	Max	68	76
	Mean ± SD	37.36 ± 9.11	36.98 ± 9.15

Table 2. Vaginitis and UTI association with DMTs exposure and duration in patients with MS. B0 vaginitis (Intercept) = -12.148; B0 UTI (Intercept) = -11.154

	Number of exposureUTI (P-value)	UTI odds (Low-High) ratio	B1 time (P-value)	Number of vaginitis (P-value)	vaginitis odds (Low-High) Ratio	Vaginitis B1 time (P-value)
Beta1a	42 (0.15)	(0.97-1.70) 1.30	0.840 (0.380)	73 (0.588)	(0.77-1.68) 1.14	1.610 (0.104)
Beta1b	20 (0.001)	(1.30-2.3) 1.70	3.805 (<0.001)	21(0.144)	(0.92 -2.27) 1.44	0.603 (0.433)
Fingolimod	21 (0.002)	(1.22-2.30) 1.76	2.465 (0.009)	36(0.028)	(1.07-2.47) 1.50	1.400 (0.152)
Fumarate	11 (0.802)	(0.70-1.80) 1.14	0.175 (0.850)	11(0.110)	(0.94-3.12) 1.47	0.931 (0.3573)
Glatiramer	19 (0.020)	(1.06-2.11) 1.60	1.300 (0.152)	40(<0.001)	(1.79-3.98) 2.35	3.432 (<0.001)
Retuximab	96 (0.001)	(1.32-2.23) 1.50	2.800 (0.005)	62(0.599)	(0.77- 1.64) 1.10	0.635 (0.444)
Ocrelizumab	7 (0.110)	(0.28-1.60) 0.80	-1.505 (0.108)	5(0.656)	(0.38-1.84) 0.73	-0.910 (0.45)
Azathioprine	10 (<0.001)	(1.80- 5.60) 3.26	2.322 (0.011)	11(0.133)	(0.80- 3.62) 1.82	2.1 (0.036)
Natalizumab	23 (0.250)	(0.40-1.30) 0.74	-0.091 (0.927)	9(0.712)	(0.40-1.69) 0.85	0.96 (0.16)

adds invaluable information on risk factors of urologic infection in pwMS.

In this study, the UTI incidence drastically increased when patients were exposed to certain DMTS. In 2022 Hellgren et al., suggested that pwMS can develop UTI when exposed to rituximab (19). Moreover, Chisari et al., corroborated the evidence that exposure to rituximab can increase UTI incidence in pwMS (20). But, these studies did not investigate the effects of the rituximab's usage duration on UTI rate. Based on our study, using rituximab increases the incidence of UTI not only the exposure but also the duration. Moreover, Moiola et al., suggested that interferons, in general, do not increase the risk of UTI in pwMS (21). However, some studies illustrated that UTI could be a side of interferon β-1b treatment in pwMS (22, 23). In our study, only the exposure and the duration of interferon β-1b had a meaningful effect on UTI risk. Several factors are reported to change the prevalence of UTI infections (9, 24, 25).

Furthermore, interferon β-1a did not increase the risk of UTI. One of the serious adverse effects of Treatment with Fingolimod in pwMS is UTI (26-28). However, recent literature has not investigated treatment with Fingolimod's duration. In our study, both the exposure to and the usage duration of Fingolimod increased the rate of UTI with statistically meaningful values.

In recent literature, Glatiramer acetate was not associated with an increased risk of UTI (23, 29). However, in 2021, Cree et al., performed a randomized clinical trial to demonstrate the Efficacy and Safety of Fingolimod doses vs. Glatiramer Acetate in pwMS (30). In Cree's article, UTI was considered an adverse effect of Glatiramer acetate. Nevertheless, our study demonstrated that glatiramer acetate exposure increased the UTI rate, but its usage duration did not have any significant effect either. In 2007, Cochrane reviewed the literature and did not find any difference between the incidence of infection between the azathioprine and placebo groups in pwMS (31). Moreover, Donze et al., recommended that Treatment with azathioprine is not a risk factor for developing urinary tract infection (32). However, Donze disclosed that the association between UTI and azathioprine was not abundantly investigated. Our study demonstrated that azathioprine's exposure and duration of usage could be a risk factors regarding UTIs.

Lee et al., reviewed the side effects of Fingolimod in 2015. They concluded that vaginitis is a side effect of Fingolimod. However, others did not have the same findings in other studies (33, 34). Our study found that fingolimod exposure increases the risk of vaginitis, but fingolimod usage duration did not have any significant effect. In current literature, there is little to no evidence of glatiramer acetate as a risk factor for vaginitis (35-37). Our study demonstrated that glatiramer acetate exposure and prolonged usage could be risk factors for vaginitis.

On the other hand, in current literature, Natalizumab is a risk factor for vaginitis (35-37). Nevertheless, our study showed no evidence of risk factors for vaginitis for Natalizumab. Finally, azathioprine usage duration was a risk factor for vaginitis in our study, but there is no evidence in recent literature.

Several limitations affected this study. We could not enlist all of our patients at the beginning of our study. Therefore, all the cases were not observed for an equal amount of time. The patient provided the history of each infection. Furthermore, there were some claims of

Table 3. Association between subtypes of MS and genitourological infectious complications

	No MS	PP	RR	SP	P-value
UTI	5	10	120	48	0.061
Vaginitis	8	1	90	13	0.068
Total cases	30	34	584	150	

PP: Primary Progressive **RR:** Relapsing Remitting **SP:** Secondary Progressive

infection without the proper documentation.

Consequently, these calms were not added to the study though they may be true. Due to a lack of resources, we could not register the bacterial strain of UTI and vaginitis by urine culture and vaginal culture. Furthermore, this study could not follow the treatment of UTI and vaginitis. So future studies can investigate whether the bacterial strain in pwMS differs from regular UTI and vaginitis and its implications for their treatment. We did not study the effects of UTI and vaginitis on subgroups like children and pregnant women because of on scope of our study. We suggest a comprehensive study can be an appropriate approach to finding the effects of UTI and vaginitis on pregnant women and children to discover the long-term morbidities that these complications can accommodate.

Conclusions

MS and DMTs have a significant role in increasing the risk of UTI and vaginitis. However, these conditions are inevitable, and anticipating the infections is an inseparable part of treating PwMS. These patients should be screened regularly for UTIs and Vaginitis as complications.

Authors' contributions

All authors contributed equally.

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Conflict of interest

All authors declare that there is no potential competing or conflict of interest.

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Ethics statement

This study was approved by the Tehran University of Medical Sciences ethics committee (code: IR.TUMS.NI.REC.1400.003).

Data availability

Data will be provided on request.

Abbreviations

DMT	Disease modifying therapies
EDSS	Expanded disability status scale
MS	Multiple sclerosis
PwMS	Patient with MS
UTI	Urinary tract infection

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