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Incidence of the urological tumours in patients suffering from multiple sclerosis

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Objectives – The goal of this study was to evaluate the incidence of urological malignancies in MS patients using active screening. *Material and Methods* – A total of 495 MS patients (141 men, 354 women, age of 42 ± 13.4) were included in the study. The duration of disease was 12.3 ± 11 years, and the EDSS score was 4.3 (±2.5). Patients, regardless of specific urological symptoms, were referred for urological evaluation. The outcomes of these evaluations were compared with data from the 2009 National Oncology Register of the Czech Republic. *Results* – The standardized incidence ratio (SIR) for the whole MS study population was 38.8 (95% CI 12.6–90.6). This incidence of urological malignancies in the MS study population was higher (statistically significant) than that of the general population. The SIR for females was 66.0 (95% CI 18.0–169.1) in the MS study population, representing a statistically significant increase over that of the general female population. The increase in incidence of urological malignancies in men with MS did not reach statistical significance over that of the general male population (SIR 14.7, 95% CI 0.4–81.7). *Conclusions* – The incidence of urological cancer in MS patients as determined by active screening is significantly higher than that found in general population.

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Introduction

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system with a variable course and rate of progression. MS is the most common immune-mediated disease in Europe, with a prevalence of 30–150/100,000 people (1). The currently employed immunosuppressive (IS) and immunomodulative (IM) therapies have proven effective in lowering the risk for disease exacerbation and disability, thereby improving quality of life for those affected (2). It is theoretically possible that alteration of the immune system (by the therapeutic medications or the disease itself) could lead to an increased incidence of malignancy in patients with MS, but the literature on the subject is inconclusive. Increased cancer risk has been documented in patients suffering from various autoimmune diseases, as well as those using systemic IS and IM therapies following allotransplantation, but the specific risk of malignancy as it pertains to MS has not been conclusively addressed (3). The most prevailing opinion is that MS does not lead to an overall increase in the cancer risk. A population-based study by Nielsen et al. (4) documented a 16% overall reduction in cancer risk in men with MS, specifically citing malignancies of the digestive, respiratory and genital organs. The goal of this study was to evaluate the incidence of urogenital malignancies in patients with MS using active screening.

Materials and methods

We have conducted an active screening study of patients with MS who presented to a single, tertiary referral centre for diagnosis and treatment of the disease. The study was approved by an Institutional Review Board of the University

Hospital, Ostrava and was performed according to the Declaration of Helsinki, World Health Organization. Each subject gave informed consent before enrolment in the study. A total of 141 men and 354 women, with an average age of 42 ± 13.4 were included in the study. The average duration of the disease, as determined by first occurrence of first symptoms, was 12.3 ± 11 years. The average time since diagnosis was 11.2 ± 9 years. Three hundred twenty-three patients (62.3%) suffered from relapsing-remitting MS, 47 (9.5%) were affected by primary progressive disease and 125 (25.2%) were affected by secondary progressive disease. The average Expanded Disability Status Scale (EDSS) score of the study population was 4.3 (±2.5). Three hundred and thirty (66.7%) of patients were treated with corticosteroids, 52 (23.4%) were treated with glatiramer acetate and 45 (9%) of patients received immunoglobulin therapy. Azathioprine was used in 274 (55.3%) patients, with an average exposure time of 53.5 ± 42.4 months and a cumulative dose of 101.0 ± 73.1 g/patient. Between January 1 and December 31, 2012, all patients with MS regardless of specific urological symptoms were referred for urological evaluation. A detailed urological history was taken, followed by a full physical evaluation (including digital rectal evaluation, urinalysis, urine culture and kidney ultrasound). Prostatic specific antigen was evaluated in all men 50 years and older. Patients with abnormal findings on initial screening went on to have cystoscopy, followed by evaluation using the appropriate imaging methods or prostate biopsy. The outcomes of these evaluations were compared with the data of the 2009 National Oncology Register of the Czech Republic (www.uzis.cz). The focus was on the following diagnoses (ICD-10): C 61 – malignant neoplasm of prostate, C 62 – malignant neoplasm of testis, C 63 – malignant neoplasm of other or unspecified male genital organs, C 64 – malignant neoplasm of kidney, C 65 – malignant neoplasm of renal pelvis, C 66 – malignant neoplasm of ureter, C 67 – malignant neoplasm of bladder, C 68 – malignant neoplasm of other or unspecified urinary organs.

Unless stated otherwise, all values are expressed as mean ± standard deviation in the descriptive part of the statistics. Standardized incidence ratio (SIR) was calculated as a ratio of frequency of tumours in the MS population and expected frequency of tumours categorized with respect to age and sex derived from the incidence of tumours in the general population. The calculations were based on Poisson probability distribution of the cancer (5). 95% confidence interval (95% CI) was calculated. If 95% CI includes one, the difference in frequency of tumours in the MS and general population is not statistically significant. If 95% CI does not include one, the difference in frequency of tumours in the MS and general population is considered to be statistically significant at the level of 0.05.

Results

The active screening technique identified a total of five patients with MS with urological cancer. The characteristics of each of these five patients are summarized in Table 1. According to data from the National Oncology Registry of the Czech Republic, the overall incidence of malignant neoplasm of the kidney (C64) in 2009 was 35.4/100,000 in males and 19.4/100,000 in females. In our study population of MS patients, the incidence calculated based on the size of the study population and the number of identified kidney cancers was 709.2/100,000 in males and 282.5/100,000 in females. The incidence of malignant neoplasm of the bladder in the general population (C 67) was 36.1/100,000 in males and 13.6/100,000 in females. In the studied cohort of MS patients, the estimated incidence of bladder cancer was 0/100,000 in males and 847.5 in females. SIR for both cancers (C64 + C67) was 38.8 (95% CI 12.6–90.6). This represents a statistically significant increase in urological cancer in the MS group as compared to the general population. SIR in females for both diagnoses (C64 + C67) was 66.0 (95% CI 18.0–169.1), representing a statistically significant increase in urological cancer in female patients with MS as compared to that of the general female population. The difference in incidence for both diagnoses (C64 + C67) in men with MS as compared to the general male population (SIR 14.7, 95% CI 0.4–81.7) did not reach statistical significance. Age-specific incidence of the urological cancer (C64 + C67) in patients with MS and in the general population is summarized in Table 2.

Discussion

MS is one of the most common neurological diseases, and because the resulting demyelination affects innervation of the lower urinary tract in 35–97% of cases, a urologist is frequently involved in the interdisciplinary care of these patients (6). It is therefore surprising that only limited attention has been given to investigating the possibility of increased urological malignancy

Table 1 Characteristics of patients with MS with urogenital cancer

Patient	Female 58 years old	Female 46 years old	Female 65 years old	Female 46 years old	Male 35 years old
Tumour type	C 67	C 67	C 67	C 64	C 64
Tumour histology	Moderately differentiated urothelial carcinoma	Moderately differentiated urothelial carcinoma	Muscle- invasive poorly differentiated urothelial carcinoma	Moderately differentiated renal cell carcinoma	Well-differentiated renal cell carcinoma
MS characteristics					
MS course	Secondary progressive	Secondary progressive	Secondary progressive	Primary progressive	Relapsing-remitting
Time since first symptoms (years)	20	6	32	12	12
Time since MS diagnosis (years)	10	6	32	12	12
EDSS	7	7	6.5	7	3
MS treatment					
Corticosteroids	Yes	Yes	Yes	Yes	Yes
Azatioprine	Yes	No	Yes	Yes	No
Mitoxantron	Yes	Yes	No	No	No
Interferon	No	No	No	No	Yes
Glatiramer acetate	No	No	No	No	Yes
Immunoglobulins	No	No	No	No	No

Table 2 Age-specific incidence of the urogenital tumours (C64 + C67) in the patients with MS and general population

	Study population				General population	
Age	Number of MS patients (*n*)	Distribution of MS patients (age groups) (%)	Number of tumours/ age group (*n*)	Tumour incidence/100,000	Tumour incidence/100,000	Expected frequency of tumours
0–4	0	0	0	0	1.57	0
5–9	0	0	0	0	0.41	0
10–14	0	0	0	0	0.12	0
15–19	16	3.23	0	0	0.18	0.000029
20–24	34	6.87	0	0	0.38	0.000129
25–29	55	11.11	0	0	0.77	0.000424
30–34	48	9.7	1	2083.3	1.76	0.000845
35–39	71	14.34	0	0	4.47	0.003174
40–44	58	11.72	0	0	10.3	0.005974
45–49	63	12.73	2	3174.6	22.1	0.013923
50–54	60	12.12	0	0	40.56	0.024336
55–59	44	8.89	1	2272.7	63.78	0.028063
60–64	25	5.05	1	4000	94.33	0.023583
65–69	11	2.22	0	0	124.21	0.013663
70–74	3	0.61	0	0	150.81	0.004524
75–79	4	0.81	0	0	161.75	0.00647
80–84	1	0.2	0	0	160.09	0.001601
85+	2	0.4	0	0	143.38	0.002868
Total	495	100	5			0.129605

in these immune-compromised patients. A study performed by Lebrun et al. in 2011 did not identify an increased risk of malignancy in patients with MS, but the authors did conclude that patients receiving IS therapy had a 300% increase in cancer risk compared to those receiving alternative treatments. This same study reported that in patients with MS receiving IS therapy, urogenital malignancies are the fourth most common cancer (7). These findings are further supported by Achiron et al., who concluded that MS patients who did not receive IS or IM therapy had a lower risk of developing cancer than that of the general healthy population. These authors point to the possibility that IS or IM therapy could eliminate the immunoprotective effect of MS (8). Both of the aforementioned studies presented data that was extracted from oncologic registers, meaning that only the patients who were symptomatic were included in their analyses. Our study focused on the incidence of urological malignancies in all patients with MS. We performed active screening using the algorithm outlined by the European Association of Urology Guidelines (9, 10). All patients with MS, including those who did not present with symptoms of lower urinary tract

disease, were included in our study group. Even using this relatively small sample size, we were able to identify cases of urological cancer before they presented with symptoms. All five cancers that we identified were diagnosed in asymptomatic patients, whose malignancies would not otherwise have been discovered at this stage. We therefore believe that our data provide a much more accurate picture of the true incidence of urological cancer among patients with MS. Due to the low number of identified cancers, we were unable to come to a conclusion regarding the effect of IS and/or IM therapies, as well as the correlation between disease stage and incidence of urological malignancy. It is still unclear whether the use of azathioprine increases the risk of cancer development.

Confavreux et al. (11) suggested that there is a dose–response relationship between cancer risk and long-term treatment with azathioprine. This study did not observe an increased risk of cancer during the first years of treatment. However, they did observe an increased risk after approximately 10 years of continuous treatment (or a cumulative dose above 600 g). In our study, three of five patients with detected cancer were treated with azathioprine in the MS group. Their cumulative dose was 18, 78 and 122 g, with a total exposure time of 12, 81 and 52 months respectively. According to the results from this study, which document the incidence of urological cancer in a group of patients with MS to be 38 times higher than that of the general population, further research, including larger studies to address this correlation, is warranted.

Conclusion

The incidence of urological cancer in patients suffering from MS as determined by active screening is significantly higher than that found in the healthy population. This study points out the need for further investigation as to the cause and warrants that increased attention be given to possible early signs of these diseases, such as microscopic haematuria.

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Conflict of interest

The authors declare no conflict of interests.

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