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Primary central nervous system tumors in patients with multiple sclerosis

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Abstract

Background Multiple sclerosis (MS) is a chronic neuroinflammatory disorder that can present with clinical and radiological features indistinguishable from a central nervous system (CNS) tumor. Previous studies suggest that whilepatients with MS have a reduced overall risk of cancer, they may have an increased risk of developing CNS malignancies.

Methods In this cross-sectional observational study, we investigated the prevalence of CNS tumors in patients with MS using data from the Isfahan MS clinic registry between 2020 and 2023 who had been diagnosed with primary CNS tumors following their diagnosis of MS.

Results Among the 2,280 registered patients, 36 individuals were diagnosed with CNS tumors, yielding a prevalence of 1.58%. The distribution of primary CNS tumors among these patients was as follows: 41.7% had pituitary adenomas, 30.6% had meningiomas, 13.9% had primary CNS lymphoma, 5.6% had acoustic neuroma, and the remaining cases included epidermoid cysts (2.8%), neurofibromas (2.8%), and glioblastoma multiforme (2.8%). The mean age at tumor diagnosis was approximately 45 years, while the mean age at MS diagnosis among those who subsequently developed a CNS tumor was 31.5 years.

Conclusion The overall prevalence of primary CNS tumors in our MS population was 1.58%. Meningiomas and pituitary adenomas were the most common types of CNS tumors observed in these patients. Given potential symptom overlap, new or unusual symptoms not typical of MS should be closely monitored or assessed for possible CNS malignancies.

Keywords Multiple sclerosis, CNS tumors, Brain tumors, Disease-modifying therapies

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Background

Given the widespread use of immunomodulatory therapies in individuals with multiple sclerosis (pwMS), assessing the prevalence and frequency of cancer within this population is crucial. However, studies across various registries have reported differing conclusions regarding cancer frequency. The increased frequency of CNS tumor diagnoses may be attributed to the frequent neuroimaging performed in pwMS, contributing to the phenomenon of surveillance bias [1–5]. Moreover, therapies aimed at treatment of CNS cancers such as surgery, radiotherapy, and chemotherapy, may be associated with MS progression, potentially due to the release of brain-specific antigens that could trigger or accelerate autoimmunity [6].

Primary tumors of the CNS (ptCNS) are biologically and genetically diverse, representing distinct categories, all of which are exceptionally rare. There are approximately 100 subtypes of a total of 29 histological variants of ptCNS accounting for 3% of all cancers. Nevertheless, mortality in CNS tumors is high and life expectancy depends on the patient's age, tumor location, and histology. Glial cell tumors are the most common type of CNS neoplasms [7–10].

The purpose of this study is to evaluate the characteristics of ptCNS in pwMS and assess the prevalence of such malignancies.

Materials and methods

This cross-sectional observational study, approved by the Isfahan University of Medical Sciences Ethics Committee (IR.MUI.MED.REC.1399.900), was conducted at the Isfahan MS clinic between March 2020 and March 2023. Inclusion criteria were: patients with a confirmed MS diagnosis based on the 2017 revised McDonald criteria; patients with a diagnosis of MS for at least one year; patients diagnosed with a CNS tumor after MS diagnosis; and patients with a confirmed CNS tumor either using biopsy, surgical excision, and/or imaging. The study included a total of 2,280 pwMS, 36 of whom were diagnosed with ptCNS. Primary CNS tumors were defined as tumors originating from the brain and the spinal cord. The study's objectives were explained via telephone and missing or incomplete data were verified and finalized. Moreover, living patients were asked to attend a follow-up visit at the clinic on a designated day.

Data were collected using a checklist comprising two sections: demographic characteristics (age, gender, etc.) and disease-related characteristics (MS type, type and location of tumor, medication use, family history, and other cancer histories).

The collected data were analyzed using SPSS software version 29. Mean and standard deviation (SD) were used for representing quantitative data, and distribution and frequency (as percentage) were used to describe qualitative data. The chi-square test was used to compare categorical variables. A p-value of <0.05 was considered statistically significant and, where applicable, 95% confidence intervals were reported.

Results

Thirty-six (1.58%) pwMS were diagnosed with a ptCNS tumor. Female predominance was present (97.20%), though this was not statistically significant compared to the overall sex distribution in our MS population (p-value = 0.056). Patients with a diagnosis of ptCNS had a mean age of 45.47 years at the time their tumor was diagnosed and 31.47 year at the time of their MS diagnosis. None of the patients with concurrent ptCNS had primary progressive MS. Table 1 represents a summary of patients' baseline data and disease related features.

Interferons (IFNs) were the most commonly used medications among pwMS and concomitant ptCNS during our study period. IFN beta-1a and IFN beta-1b accounted for 61.1% and 13.9% of the total medications, respectively. Among patients with ptCNS receiving IFN beta-1a, one patient received the medication every other day, while the remainder were on a weekly dosage schedule. Only one patient had secondary progressive MS (SPMS), a 48-year-old female diagnosed with acoustic neuroma, and with a positive family history of MS in her sister. The only male patient, aged 39 years, had relapsing-remitting MS (RRMS) and was diagnosed with pituitary adenoma. Pituitary adenomas and meningiomas were the most common CNS tumors observed in our MS population. Two patients with ptCNS one with primary CNS lymphoma (PCNSL) and another with glioblastoma multiforme- were deceased at the time of our study. A summary of tumor types and locations is provided in Table 2.

All tumors were identified following the onset of new symptoms that necessitated additional imaging. The most common symptoms associated with brain tumor included focal neurologic deficits (66.7%), persistent headaches (22.2%), and seizures (11.1%).

Discussion

In this single-center study, we have presented a series of patients with concurrent ptCNS and MS. In our cohort of MS patients, 1.58% were found to have ptCNS. This frequency is notably higher than the general population prevalence reported in the literature ranging from 0.13–0.22% [11,12]. In general, incidence, prevalence, and survival rates for CNS tumors vary by histologic type, age at diagnosis, gender, and race. For instance, the frequency of meningiomas in females is considerably higher than what is observed in men [13]. Other tumor types such as glioblastomas are more commonly observed in men.

Table 1 Patients demographics and baseline disease characteristics

Variable	Patients with ptCNS (*n* = 36)	Patients without ptCNS (*n* = 2244)	*p*-value
Age (mean ± SD)	31.47 ± 9.10	29.18 ± 8.96	*0.13*
At MS onset	45.47 ± 8.08	--	
At tumor diagnosis (mean ± SD)			
Sex (n,%)	1 (2.8%)	309 (13.8%)	*0.056*
Male	35 (97.2%)	1935 (86.2%)	
Female			
Type of MS (n,%)	35 (97.2%)	1980 (88.20%)	*0.23*
RRMS	1 (2.8%)	188 (8.40%)	
SPMS	0 (0)	76 (3.40%)	
PPMS			
Type of Medication (n,%)	22 (61.1%)	351 (18.3%)	*< 0.001*
INF beta-1a	5 (13.9%)	239 (12.4%)	
INF beta-1b	3 (8.3%)	344 (17.9%)	
Rituximab	1 (2.8%)	63 (3.3%)	
Glatiramer Acetate	3 (8.3%)	514 (26.7%)	
Dimethyl Fumarate	1 (2.8%)	209 (10.9%)	
Fingolimod	1 (2.8%)	202 (10.5%)	
Teriflunomide			

IFN: Interferon, MS: multiple sclerosis, PPMS: Primary Progressive MS, ptCNS: Primary tumor of the CNS, RRMS: Relapsing-remitting MS, SD: Standard deviation, SPMS: Secondary Progressive MS

Table 2 Characteristics of primary tumors of the CNS in patients with MS

Tumor type	Location (*n*)	Number of tumors (*n*,%)	Age at tumor diagnosis	Sex (*n*,%)		Survival outcome (*n*,%)	
				Male	Female	Alive	Deceased
Adenoma	Pituitary	15 (41.66)	44.20 ± 8.10	1 (2.77)	14 (38.88)	15 (41.66)	0 (0)
Meningioma	Parasagittal (3), Parietal (3), Temporal (2), Posterior fossa (1), Parieto-occipital (1), Optic nerve (1)	11 (30.55)	46.91 ± 9.07	0 (0)	11 (30.55)	11 (30.55)	0 (0)
PCNSL	Fronto-parietal (3), Thoracic spinal cord (1), Corpus Callosum (1)	5 (13.88)	47.40 ± 8.62	0 (0)	5 (13.88)	4 (11.11)	1 (2.77)
Acoustic Schwannoma	Cerebellopontine angle	2 (5.55)	47.50 ± 0.70	0 (0)	2 (5.55)	2 (5.55)	0 (0)
Epidermoid cyst	Diencephalon	1 (2.77)	35	0 (0)	1 (2.77)	1 (2.77)	0 (0)
Neurofibroma	Cervical spinal cord	1 (2.77)	40	0 (0)	1 (2.77)	1 (2.77)	0 (0)
Glioblastoma multiforme	Frontal	1 (2.77)	51	0 (0)	1 (2.77)	0 (0)	1 (2.77)
Total		36 (100)	45.47 ± 8.08	1	35	34	2

Simultaneous development of primary CNS tumors and MS is exceptionally rare and only a limited number cases have been reported. Inference on whether concurrent primary CNS tumors and MS extend randomly or have common pathophysiological mechanisms is still under debate [10]. Underlying pathologic mechanisms of both diseases can be multifactorial such as viral infections, persistent and long-term inflammation, neoplastic transformation, and influence of neurotropic growth factors. On the other hand, neoplastic and demyelinating processes can occur in conjunction in both diseases. Furthermore, diagnostic difficulties exist as clinical features and neuroimaging characteristics are unspecific in most cases [10].

Nonetheless, studies have shown an increased rate of cancer types other than CNS malignancies in pwMS. Immunomodulatory therapy in such cases may potentially affect the risk of cancer [9]. However, data regarding the incidence of cancer in MS patients are inconsistent. In fact, several studies have shown that the risk of urinary tract and nasopharyngeal cancers are elevated [14]. Other studies report that this group of patients have a lower risk of initiation and progression of several cancer types such as prostate, ovarian, breast, gastrointestinal cancers, and lymphomas which may also be linked to disease modifying therapies [15–17]. Indeed, immunomodulatory drugs suppress the immune system by depleting lymphocytes, redirecting lymphocyte trafficking, and blocking lymphocyte response pathways leading to increased risk of infections and cancer [18].

B cells in pwMS secrete various types of pro-inflammatory cytokines such as Interleukin (IL)-6, tumor necrosis factor-alpha, and lymphotoxin. Reduction in anti-inflammatory cytokines such as IL-10 is also evident. In MS and other related conditions, peripheral immunity is activated via the release of pro-inflammatory cytokines. Elevated serum levels of these cytokines potentially correlate with neuroendocrine and neurochemical alternations

that eventually lead to an increased susceptibility to neurological disorders and malignancies. Pro-inflammatory cytokines alter cellular homeostasis and epigenetic plasticity, triggering changes in gene expression of various oncogenic-related genes [19–25].

Interferon is an injectable disease-modifying therapy (DMT) that is commonly used in MS and certain malignancies (leukemia, lymphoma, etc.). Studies have also pointed to the potential role of IFNs in the treatment of cancers particularly hematologic cancers and solid cancer of the head and neck [26–28]. The most common clinical side effect of interferon therapy is neurological toxicity and behavioral and cognitive changes mainly affecting the quality of life [27, 29]. Although interferon was for long proposed as an antiviral agent without any effects on normal cellular metabolism, studies have shown normal cell proliferation and intracellular function compromise in patients taking the medication. Moreover, the effects of interferon on cytokine profiles, immune system tolerance, and critical cellular signaling pathways, may lead to unrestricted cellular proliferation with an end product of cancer [30]. This is in line with our study that CNS tumors were more common in pwMS taking weekly interferon injections (table-1). This potential relationship between interferon-based therapies and increased incidence and progression of CNS tumors, especially meningiomas, may be related to the long-term effects of platelet-derived growth factor upregulation and downregulation of tumor antigen presentation along with T-cell tumor surveillance [31, 32]. However, current knowledge on the biological effects of interferons in the pathogenesis of CNS tumors in patients with MS is limited.

Pituitary adenoma and meningioma were the two most common tumors observed in pwMS (38.46% and 28.20%, respectively) (Table-2). The definitive link between MS and pituitary adenoma is still debated. Generally, as previous studies have shown, the coincidence of pituitary adenoma and MS has been found in many patients. Possible role for prolactin, an endocrine neuronal peptide with strong immune system properties, has been suggested in MS and disease attacks induced by hyperprolactinemia have been reported. On the one hand, prolactin has potent immunomodulatory properties, with mild hyperprolactinemia leading to increased risk of autoimmune diseases, including MS. On the other, prolactin can trigger an inflammatory state, and imbalance between prolactin and other hormones can trigger immunologic intolerance, a state apt for autoimmunity and cancer [33, 34].

Limitations

Our study has several limitations that should be considered when interpreting the results. First, the relatively small number of primary CNS tumor cases (36) within the cohort of 2,280 pwMS may limit the generalizability of our findings. Second, the retrospective design of the study may introduce selection bias or inaccuracies due to incomplete medical records or variations in diagnostic criteria over time. Third, we did not assess the potential confounding effects of treatment modalities for MS, such as immunomodulatory or immunosuppressive therapies, which could influence the development of CNS tumors. Finally, our findings are limited to a single population and may not be directly applicable to other demographic or geographic groups due to differences in genetic, environmental, or healthcare factors.

Conclusion

The overall prevalence of primary CNS tumors in our MS population was 1.58%. Meningiomas and pituitary adenomas were the most common types of CNS tumors observed in these patients. Given potential symptom overlap, new or unusual symptoms not typical of MS should be closely monitored or assessed for possible CNS malignancies. Further studies could elucidate the potential underlying mechanisms of CNS tumor development in patients with MS and explore potential connections with disease-modifying therapies.

Abbreviations

CNS	Central nervous system
ptCNS	Primary tumors of the central nervous system
pwMS	Patients with multiple sclerosis
RRMS	Relapsing remitting multiple sclerosis
SPMS	Secondary progressive multiple sclerosis
DMT	Disease-modifying therapy
IL	Interleukin
IFN	Interferon

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Author contributions

MS and ME conceptualized and designed the study. AAS and FDF wrote the primary draft of the study, collected relevant data, and analyzed the data. SS analyzed the data and revised the primary draft. All authors have read and approved the final manuscript for publication.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Isfahan University of Medical Sciences ethical committee (IR.MUI.MED.REC.1399.900) and proper informed consent was taken from patients for participation in our study. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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