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Original Article

Prevalence of benign tumors among patients with multiple sclerosis

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Abstact. Multiple sclerosis (MS), an inflammatory autoimmune disease, affects almost 1% of world's population in which myelin sheaths of neurons are targeted by immune cells. Association of different factors and diseases with MS provides new insights into possible pathogenesis and treatment for this disease. In this regard, we investigated the association of benign tumors with MS disease by studying total Isfehan multiple sclerosis (TIMS) records for MS patients registered in Isfahan Multiple Sclerosis Society (IMSS) who had developed any kind of benign tumors whether before MS diagnosis or after it. This study was performed in Isfahan province, third large province of Iran, with 4,815,863 populations located 1590 meters above sea level between latitudes 30 and 34 degrees north of the equator, and longitude 49-55 east. Among 4950 registered patients, 28 patients were discovered to have three types of benign tumors; pituitary adenoma in 22, meningioma in 5 and lipoma in 1 patient. The incidence rate of developing pituitary adenoma and meningioma were higher than in general population (OR 95%CI: 1.110; range: 0.731-1.685 and 1.035; range: 0.431-2.487 respectively) but these findings were not statistically significant (p= 0.624 for pituitary adenoma and p= 0.939 for meningioma). But the incidence rate for lipoma was lower among MS patients (OR 95%CI: 0.020; range: 0.003-0.143) which was statistically significant (p <0.001).

Keywords: Multiple sclerosis, benign tumors, pituitary adenoma, meningioma, lipoma

Introduction

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease of central nervous system (CNS) and a leading cause of neurologic disability in young adults. Although, the exact etiology of MS still remains unknown but based on studies crucial role of immune system and immune cells in targeting myelin sheaths of neurons have been proven. Autoactivated T-cells and exacerbated cellular immune responses are considered as potential causes of MS. Also imbalanced Th1/Th2 cell population and increased Th1 inflammatory cytokines play a pivotal role in MS pathogenesis [1]. The prevalence of MS varies widely in different geographical regions. For instance, higher latitude is associated with higher prevalence of MS based on what Kurtzke reported [2]. Iran is located between latitude 32°00 ′ N longitude 53°00 ′ in Middle East with increasing both incidence and prevalence of MS especially in females. Benign tumors are mass of tissue without the ability to invade neighboring tissues or metastasize. Most of benign tumors are surrounded by a capsule and can be recognized by different mechanisms including detecting tumor associated antigens, magnetic resonance image (MRI), clinical symptoms and other methods. Pituitary adenoma, meningioma and lipoma are all considered as benign tumors with different incidence rates. Pituitary adenoma affects almost 0.4% of general population, meningioma has incidence rate of 97.5 per 100,000 and lipoma affects 1% of general population.

In this study we endeavored to compare the incidence rate of growing benign tumors in public with MS patients in order to determine whether incidence rate of benign tumors in those who suffer from MS is higher than general population or not.

Materials and Methods

Our study was performed in Isfahan which is the third large province of Iran (province (107 003 km^2). Isfahan is located in the center of Iran with 1590m above sea level between latitudes 30 and 34 degrees north of the equator, longitude 49–55 east. The climate of Isfahan is dry and temperate with a mean of daily temperature which varied widely from 5.3 in January to 27.2 in August. The population of Isfahan was estimated 4,815,863 according to the Iranian Central Bureau of Statistics (ICBS) reports.

The socioeconomic proportions, current demographic characteristics and lifestyles are all the same like other

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TABLE 1
CLINICAL AND PARACLINICAL FEATURES OF THE CASES

Sex		
Female	27	96.4
Male	1	3.6
First sign		
Weakness	7	25
Sensory	4	14.3
Visual	14	50
Cerebellar	3	10.7
EDSS		
≤2	25	89.3
>2	3	10.7
MS type		
RR	26	92.9
PP	1	3.6
SP	1	3.6
Medication		
Cinovex	14	50
Imuran	5	17.9
Betaferon	7	25
Avonex	2	7.1
Cancer family		
Present	27	96.4
Absent	1	3.6
Tumor type		
Meningioma	5	17.9
Lipoma	1	3.6
Pituitary adenoma	22	78.6

parts of the country. The major health services in this province consist of private physicians and hospitals, district health centers, government, university hospitals, and clinics.

In this retrograde study, we reviewed the case records of those patients diagnosed with definite MS based on McDonald criteria [3] who were also residents of Isfahan. All these patients had been previously registered in Isfahan Multiple Sclerosis Society (IMSS), the only referral center for Isfahanian MS patients. The diagnosis of patients is performed by the neurologists of IMSS based on the 2010 version of International panel in MS diagnosis which is commonly known as McDonald. McDonald criteria are made up of three distinct broad groups: "definite MS," "possible MS," and "not MS." Definite MS diagnosed patients were included in our study. Also disability of these patients was assessed by Expanded Disability Status Scale (EDSS) [4].

Due to the supports for insurance, laboratory investigations, treatment, and rehabilitation, all diagnosed MS patient from all health sectors in Isfahan province has been registered by IMSS since 2005. Also it should be noted that the information of some small number of patients who prefer private care services might possibly be missed. The case records of patients, which were used as data base in our study, include glorious information taken from each patient by neurologists of IMSS such as: background variables, clinical records including disease pattern (relapsing-remitting MS (RRMS), primary progressive MS (PPMS), secondary-progressive MS (SPMS), and progressive-relapsing MS), symptoms, signs and relapse history (date, duration and type), therapeutic protocols, EDSS, and any significant complication in patients' status.

We first checked the total Isfehan multiple sclerosis (TIMS) records looking for MS patients with benign tumors diagnosed at any stage of their life span by oncologists. We investigated these records for those patients who had developed any kind of benign tumors whether before MS diagnosis (by searching in clinical history records) or after it (by searching in IMSS follow-up records). All detected patients were called back to IMSS center for final clinical/paraclinical examinations and signing the written informed consent. The study was also approved by the ethic committee of the university.

We then compared by $\chi 2$-statistics the rate of developing benign tumor in general population with the frequency of benign tumors in MS population in order to determine whether the association of MS and benign tumors in these diagnosed patients happened merely incidental or not. The size of this population was estimated by summation of pituitary adenoma, meningioma and lipoma incidence ranges which are 0.4% for pituitary adenoma, 97.5 in 100,000 for meningioma and 1% for lipoma respectively serving as the upper and lower values worldwide respectively multiplied by Isfahan population resulting the incidence rate of developing benign tumors among general population.

Data were analyzed by SPSS, version19. Results have been reported as a mean (±SD) and number (percent). All tests were two-tailed, and a P-value of <0.05 was considered as significance threshold.

Results

Of the 4950 registered MS patients in IMSS, three types of benign tumors (meningioma, lipoma and pituitary adenoma) had been developed in 28 MS patients (0.565%) with the mean age of 33.61±6.93 years. Their MS condition was considered RRMS in 92.9% of them with the EDSS ≤2 with frequency of 89.3% (n=25) and half of patients (50%) were on therapeutic period with cinovex. 27 (96.4%) of these patients were female adults and only one patient (3.6%) was male. The first symptom of MS observed in these patients was visual, weakness, sensory and cerebellar (Table 1). From these 28 MS patients, five patients (17.9%) had developed meningioma, one (3.6%) diagnosed with lipoma and 22 of these MS patients (78.6%) had been developing pituitary adenoma. It should be noted that 27 of these patients (96.4%) had familial backgrounds.

The results from comparing rates of developing benign tumor among patients with MS and non-MS yielded the incidence rate of developing meningioma to be 1.035 but this result was not statistically significant due to the p=0.939. Another result of our study showed that the incidence rate for lipoma was 0.020 among MS patients which was statistically meaningful (p<0.001). This result suggests that lipoma occurs more likely in MS patients than in general population. For pituitary adenoma, the results indicated an incidence rate of 1.110 which was not

TABLE 2
COMPARISON OF PREVALENCE RATE OF BENIGN TUMORS BETWEEN MS PATIENTS AND GENERAL POPULATION

Tumor	MS		OR	P-value
	Present	Absent	(95%CI)	
Total No.	4950	4810913		
Meningioma				
Present	5	4695		
Absent	4945	4806218	1.035 (0.431-	0.939
Lipoma				
Present	1	48158		
Absent	4959	4762755	0.02 (0.003-0.143)	<0.001
Pituitary adenoma				
Present	22	19263		
Absent	4928	4791650	1.110 (0.731-	0.624

TABLE 3
SURVEYING FACTORS AFFECTING BENIGN TUMORS

Tumor type	Factor	Beta	OR (95%CI)	P-value
Meningioma				
	Age	0.408	1.51 (0.951-24.012	0.033
	MS onset age	0.379	1.46 (0.975-22.188)	0.036
	EDSS	2.08	8.00 (0.823-77.82)	0.043
	Cancer family	24.193	30.01 (0.901-1.011)	0.20
Pituitary adenoma				
	Age	-0.222	0.801 (0.66-0.968)	0.021

considerable because of the p-value of 0.624 (Table 2).

A survey on the risk factors effective in developing the three reported benign tumors using "logistic regression" with "background" method indicated that the following factors can be effective in developing meningioma: age, MS onset age, EDSS and familial background serving as the most important of all. The same survey performed for pituitary adenoma demonstrated that the only effective factor is age with an adverse relation. Due to only one reported lipoma, no significant risk factor could be considered for developing this benign tumor. Age deliberations made this fact distinct that the age of MS patients with meningioma is at the higher end of our data and on the other side pituitary adenoma stands which means younger MS patients or those MS patients with lesser onset age are more susceptible for developing meningioma and the MS patients with higher years of age are more likely to develop pituitary adenoma (Table 3). Another finding of our research was that the MS disease process was low in most of MS patients (89.3%) with benign tumors based on EDSS scale (≤2) meaning they had a slow disease process.

Discussion

There have been some sporadically reports claiming the coincidence of a benign tumor and MS in the literature [5-8] which suggest a higher incidence of brain tumors in patients who suffer from MS compared to general population. Although the reason for this suggested association between the two factors is not yet definitely clear, there are some hypothesis claiming the possible association between MS and developing a benign tumor might be due to the plaques formation in the brains of patients with MS or maybe developing a benign tumor may be caused by immunosuppressive treatments taken by MS patients [9, 19]. In most reported patients, occurrence of MS is prior to developing a benign tumor with a long time gap between them but in few case reports including Markou's [11], it has been indicated that MS occurs shortly after treating a benign tumor. Our research team tried to find out the relationship between the two factors. In this regard we studied the TIMS records of MS patients registered in IMSS in order to find any case of MS disease with any kind of benign tumors and compare it to the data about incidence rate of developing benign tumor in Non-MS Patients. Since we couldn't find any survey in which the incidence rate of developing benign tumor in Isfahan general population had been determined, we compared our findings with the world's incidence rate for benign tumors (i.e. pituitary adenoma: 0.4%, meningioma: 97.5 in 100,000 , lipoma: 1%). AS mentioned above, three types of benign tumors (i.e. meningioma, pituitary adenoma and lipoma) were found in 0.565% of MS patients. Data analysis demonstrated a higher incidence rate of meningioma and pituitary adenoma among MS patients but these findings were not statistically meaningful. On the other hand, incidence rate of lipoma was found to be significantly lower among MS patients. Furthermore, a survey on disease process and severity based on final EDSS score indicated a low disease process in majority of MS patients who also suffer from developing benign tumor. Taken together, these findings help us to conclude that there may not be a direct correlation between these two diseases, although they may affect each other in some ways.

It's been well documented in many research studies that MS is an autoimmune disease of central nervous system in which immune cells attack to myelin sheaths of nerves [12]. Both T-cell and B-cell activation with antibody formation have been shown to play a role in MS pathogenesis [13]. On the other hand, developing tumors is highly associated with a defect in immune system or weakness in any aspect of immune responsibility against tumors. So there can be a relationship in developing tumors and MS disease.

Pituitary adenoma is a benign tumor of pituitary glandin the brain that is mostly associated with higher amount of prolactin production. Prolactin production is regulated by some regulatory hormones produced in hypothalamus including: thyrotrophin releasing hormone (TRH), somatostatin (GHIH) and prolactin inhibitory hormone (PIF). Prolactin is well known for its effects on breast feeding and milk production (14) but it has some other roles in immune system and immune cell maturation by its receptors spread throughout immune cells such as T-cells and B-cells [15, 16]. Prolactin is recently known to play an important role in some autoimmune diseases such as systemic lupus erythematous (SLE), rheumatoid arthritis (RA), Sjogren's syndrome (SS), Hashimoto's thyroiditis (HT), Celiac disease (CD), Graves' disease (GD), lymphocytic hypophysitis (LH), Addison's disease (AD), diabetes mellitus (DM) type I, and MS [17-19]. As some recent studies indicate, prolactin level in serum and CSF is

increased in of MS patients [19-21]. Furthermore, they claim that higher levels of prolactin in MS patients are associated with higher EDSS score. On the other hand, some researchers including Markianos report no correlation between prolactin level and the disease [22].

Although studies on the correlation between pituitary adenoma and MS hasn't yet drawn much attention among researchers and the definite correlation between MS and pituitary adenoma is still lacking, in this article we found higher incidence of pituitary adenoma in MS patients compared to with general population. The effects of prolactin in MS might be due to, at least in part, progressing inflammation and inflammatory processes. The association of higher level of prolactin and autoimmune diseases is mediated via different influences of prolactin on different aspects of immune system. Increased level of prolactin has been demonstrated to interfere with B-cell tolerance, clonal deletion and decreasing the threshold for activation of anergic B-cell

As Saha et al. [23] indicated, hyperprolactinemia interferes with BCR-mediated deletion, receptor editing and anergy as three main mechanisms of B-cell tolerance which can induce production of autoreactive B-cells. Another mechanism that prolactin helps to improve autoimmune diseases is by enhancing the release of thymocytes from thymus and activating Th1 lymphocytes and producing inflammatory cytoines such as INF-g [24, 25]. Other inflammatory cytokines, in particular, IL-1, TNFa, IL-6 and IL-13 are able to induce prolactin from pituitary which in part helps more inflammatory responses of immune system. As shown by Matera, increased antigen presenting activity by dendritic cells and expression of CD40 cells are also induced by prolactin that in turn improves autoimmune activity [26]. Taken together, these findings demonstrate a considerable influence of prolactin on improving inflammation and autoimmune diseases such as MS.

We indicated in our study that the incidence of pituitary adenoma as a benign tumor is higher among MS patients than in general population but this increased risk was not statistically significant. Few confirmed risk factors have been associated with meningiomas which account for 38% and 20% of all cranial tumors in women and men respectively [27]. Many researchers believe that autoantibodies play an important role in pathogenesis of meningiomas [28]. Although the association of meningioma with MS is not yet completely vivid, Batay and Al-Mefty [29] believe that occurrence of meningioma is correlated with MS and the exacerbation of meningioma was observed during interferon treatments as it was observed by others too[30]. They also believe that therapies with type-1 interferon could be the possible cause of meningioma growth due to autoimmune aggression with lymphocytic infiltration [29]. Association of CNS tumors growth including meningioma and use of glatiramer acetate was also suggested by kleinpaul and colleagues [31] in a case report study. On the other hand Costa et al. [32] suggest that meningioma symptoms are usually remitted after corticosteroid therapy in MS patients. In this article our research team indicated a higher incidence rate of meningioma in MS patients but these results were not statistically considerable. In another study performed by Schneider and colleagues [33], it's been shown that meningioma is associated with some other diseases such as diabetes mellitus and hypertention but not with rheumatoid arthritis.

The higher incidence of meningiomas in women (2:1) can be caused by hormonal factors including estrogen and progesterone however consequently some suggest that administering oral contraceptives and/or hormone replacement therapy can cause meningiomas [34, 35]. Data from case-control and cohort studies indicate controversial results about the impact of oral contraceptive use and risk of meningioma. While some demonstrated increased risk of meningioma associated with the use of long acting hormonal contraceptives [36], others show no definite correlation [34].

Similar studies with different results have been performed to consider the association between the use of contraceptives and MS disease [37-39]. Some of these studies resulted in positive effects of oral contraceptive use on MS onset and severity while others found no considerable relation. Optic nerve sheath meningiomas are formed in the anterior visual pathway resulting in visual deficit, color blindness and finally complete loss of vision [40, 41] with some similarity in symptoms with MS.

Another finding of our study was significant lower incidence of lipoma among MS patients. Lipomas are benign tumor of mature adipocyte tissue mostly found in gastrointestinal tract especially colon. One important characteristic of lipomas is that these types of neoplasm are often asymptomatic and are found incidentally at radiological investigation, colonoscopy, surgery or autopsy [42, 43]. Furthermore, lipomas are painless and do not draw much attention in public which results in ignorance. Therefore, not all of patients with lipoma visit doctors or go to therapeutic centers meaning lower reported cases. The correlation between lipoma and MS disease is not completely clear yet and much more basically researches are demanded in order to consider the molecular relation between MS and lipoma.

In conclusion, of the three types of benign tumors found in MS patients in our study, two (pituitary adenoma and meningioma) were considered to have higher incidence rate among those suffering from MS than in general population but these findings were not statistically significant. On the other hand, lipoma had a lower incidence rate in MS patients which was statistically significant. Association of those benign tumors with MS disease which was also reported in other studies could be explained via reviewing the mechanisms and outcomes of these tumors but further studies are required for definite explanations.

Conflict of interest

The authors declare no conflicts of interest.

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