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Research Article

Risk Factors and Clinical Profiles of Multiple Sclerosis with Extent of Disability: A Study from Tertiary Care Center

Jaydip Ray Chaudhuri[1], Rukmini Mridula K[2] and Srinivasarao Bandaru VCS[1,3]*

[1]*Department of Neurology Yashoda hospital, Hyderabad, India.*

[2]*Department of Neurology City Neuro center Hyderabad, India.*

[3]*Department of Clinical Research Yashoda Group of hospitals Hyderabad, India.*

Corresponding Author Information

Srinivasarao Bandaru VCS

Department of Neurology and Clinical Research, Yashoda Hospital Hyderabad, India, Mobile: +91 9441266519, Fax: 91 040 -23319999.

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ABSTRACT

Background: Multiple sclerosis (MS) is a neurological disorder involving central nerves system. MS can affect both genders, more commonly women and younger adults. MS is associated with various risk factors and can lead to significant disability and poor quality of life.

Aim: The present study is to investigate, the clinical profile, risk factors and assess their correlation with disability using Expanded Disability Status Scale (EDSS).

Methods: This prospective observational study recruited 102 patients with MS at department of Neurology, Yashoda hospital, Hyderabad, India. All patients met the McDonald's 2010 criteria for MS. Risk factor evaluation was done. EDSS was done for all patients. Analysis was performed after dichotomizing patients based on EDSS (≤ 3.0 and ≥ 3.5 EDSS).

Results: Out of 102 patients, women were 60 (58.2%), mean age was 47.2 ± 13.4 years. On clinical symptoms, optic neuritis was seen in 70 (68.6%), sensory involvement in 46 (45%) and bladder symptoms in 33 (32.3%). Associated peripheral nerve involvement was seen in 40 (39.2%). Hypertension was noted in 13 (12.7%), diabetic mellitus in 18 (17.6%), smoking in 38 (37.2%), alcoholism in 35 (34.3%), obesity in 28 (27.4%), 25-hydroxyvitamin D deficiency in 57 (55.8%), and non-vegetarian diet in 76 (74.6%) patients. In MS subtypes, 68 (66.6%) had RRMS, 5 (4.9%) had SPMS and 29 (28.4%) CIS. We compared the risk factors between patients with mild disability (> 3.0 EDSS) and severe disability (> 3.5 EDSS). Women (p=0.002), age>40 years (p=0.005) smoking (p=0.01), alcoholism (p=0.01), obesity (p=0.002), 25-hydroxyvitamin D deficiency (p=0.001) and vegetarian diet (p<0.0001) were significantly associated with severe disability.

Conclusion: In our study, we established female gender, age>40 years, smoking, alcoholism, obesity, 25-hydroxyvitamin D deficiency and vegetarian diet to be associated with severe disability in patients with MS.

Keywords

Risk factors, Clinical profile, Multiple sclerosis.

Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease associated with central nervous system [1]. MS affects more than 2.8 million people around the world, with an estimated overall prevalence of 35.9 per 100,000 populations [2] and higher prevalence in Europe (142.81 per 100,000) and lower prevalence in the Western Pacific region (4.79 per 100,000) [3]. In India, MS prevalence has increased from 1.33 to 8.35/100,000 [1]. Recent studies have shown an increase in the prevalence of the disease across Asia, American Europe, and Latin America [2]. Different factors, such as smoking, environmental factors such as Epstein-Barr virus infection, latitude of residence, vitamin D status, and genetics, have been considered as associated risk factors for MS [4]. Autoimmunity along with several environmental risk factors play a vital role in its aetiology; however, the precise pathogenic mechanisms that bring on the development of MS are still elusive [5]. MS affects both genders and all age groups, especially younger women. The most commonly affected sites are the optic nerve, brain stem, spinal cord, and periventricular white matter, and it leads to both cognitive and physical disability among the affected. The current study aims to investigate the clinical profile, risk factors, and subtypes of MS.

Material and Methods

We prospectively recruited 102 patients with MS from the department of Neurology at Yashoda hospital, which is a tertiary care centre and post-graduation teaching hospital in South India. This study was approved by the Institutional Ethics Committee, and informed consent was obtained from all patients during the study period between March 2012 and February 2022.

Inclusion and Exclusion Criteria

All MS patients met the 2010 McDonald's criteria; diagnosis was confirmed by an MS specialist based on clinical history; magnetic resonance imaging of the brain and spinal cord; Evoked potentials visual (VEP) and auditory (BAEP) and cerebrospinal fluid analysis (elevated immunoglobulin G [IgG] index or 2 or more oligoclonal bands). Neuromyelitis optica (NMO) patients were included in the study. MS patients who did not meet McDonald's 2010 criteria and had a history of stroke or cardiac disease, or vasculitis, endocrinological dysfunction, substantial abnormalities in hematologic, hepatic, renal, or metabolic dysfunctions, any condition predisposing to hypercalcemia, or nephrolithiasis were excluded from the study.

MS Subtypes

Based on clinical and radiological examination, MS subtypes are Relapsing-Remitting Multiple Sclerosis (RRMS), Progressive-Relapsing Multiple Sclerosis (PRMS), Secondary-Progressive Multiple Sclerosis (SPMS), and Clinically Isolated Syndrome (CIS).

Risk factor evaluation

Demographic data (age, sex), level of education, socioeconomic status, past medical history, and physical and neurologic examination were evaluated by a senior neurologist. Definitions for hypertension, diabetes, dyslipidemia, smoking, alcoholism, and obesity were mentioned in our previous paper [1].

Assessment of expanded disability status scale (EDSS)

The Expanded Disability Status Scale (EDSS) was assessed in all patients by a single neurologist with expertise in neuroimmune disorders on the day of admission.

EDSS 0: Normal neurological exam, no disability in any FS

EDSS1.0: No disability, minimal signs in one FS

EDSS1.5: No disability, minimal signs in more than one FS

EDSS 2.0: Minimal disability in one FS

EDSS 2.5: Mild disability in one FS or minimal disability in two FS

EDSS 3.0: Moderate disability in one FS, or mild disability in three or four FS, no impairment to walking

EDSS 3.5: Moderate disability in one FS and more than minimal disability in several others, no impairment to walking.

EDSS 4.0: Significant disability but self-sufficient and up and about 12 hours a day, able to walk without aid or rest for 500 m.

EDSS 4.5: Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300 m.

EDSS 5.0: Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200 m.

EDSS 5.5: Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100 m.

EDSS 6.0: Requires a walking aid, cane, crutch, etc. to walk about 100 m with or without resting.

EDSS 6.5: Requires two walking aids, a pair of canes, crutches, etc. to walk about 20 m without resting.

EDSS 7.0: Unable to walk beyond approximately 5 m even with aid, essentially restricted to wheelchairs, though wheels themselves in standard wheelchairs and transfers alone. Up and about in a wheelchair some 12 hours a day.

EDSS 7.5: Unable to take more than a few steps. Restricted to wheelchair and may need aid in transferring. Can wheel themselves but cannot carry on in a standard wheelchair for a full day and may require a motorised wheelchair.

EDSS 8.0: Essentially restricted to bed or chair or pushed-in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally, has effective use of arms.

EDSS 8.5: Essentially restricted to bed much of the day, has some effective use of arms, retained some self-care functions.

EDSS 9.0: Confined to bed. Can still communicate and eat.

EDSS 9.5: Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow and EDSS 10.0: Death due to MS.

In the present study, we dichotomized patients into those with low

EDSS score (≤ 3) and high EDSS score (≥ 3.5).

Statistical Analysis

Statistical analysis was done using SPSS 15.0 software (statistical package for the Social sciences, SPSS Inc). Mean+SD (Standed Deviation) was calculated. The paired 't' test was applied to test the differences in continuous variables. All tests were two sided and p value <0.05 was significant.

Results

Out of 102 MS patients, 60 (58.2%) were women, mean age was 47.2±13.4years (age range 19-69years) and disease duration 6-120 months. Among the clinical profile apart from motor symptoms, sensory involvement was seen in 46 (45%) and bladder symptoms were seen in 33 (32.3%), Radiological finding showed lesions in cerebellum in 58 (56.8%), brain stem in 62 (60.7%), basal ganglia in 65 (63.7%), spinal cord in 68 (66.6%), and optic nerves in 70 (68.6%), On risk factors evaluation, hypertension was seen in 13 (12.7%), diabetes mellitus in 18 (17.6%) patients, 38 (37.2%) patients were smokers, alcoholism was seen in 35 (34.3%), 25-hydroxyvitamin D deficiency was seen in 57 (55.8%), family history of MS in 6 (5.9%), history of migraine in 5 (4.9%) and non-vegetarian diet in 76 (74.6%). In MS subtypes RRMS was most common and present in 68 (66.6%), SPMS in 5 (4.9%) and CIS in 29 (28.4%) patients (Table 1).

In table 2, women (n= 35 (76%)) (p=0.002), age>40 years (n=31 (67.3%) (p=0.005)), smoking (n=23 (50%) (p=0.01)), alcoholism (n= 21 (45.6%) (p=0.01)), obesity (n=20 (43.4%) (p=0.002)), 25-hydroxy vitamin D deficiency (n=34 (73.9%) (p=0.001)), and patient having vegetarian diet (n=22 (47.8%) (p <0.0001)) were significantly associated with higher EDSS (≥3.5).

Table 1: Baseline characteristics.

Parameters	Numbers (%) (n=102)
Women	60 (58.2%)
Mean age	47.2 ± 13.4
Age range (years)	19-69
Peripheral nervous system involvement (abnormal NCS)	40 (39.2%)
Sensory involvement	46 (45%)
Bladder symptoms	33 (32.3%)
Gait disturbance,	30 (29.4%)
Disease duration (in months)	6-120
Mean disease duration	25.4 ± 22.5
Hypertension	13 (12.7%)
Diabetes Mellitus	18 (17.6%)
Smoking	38 (37.2%)
Alcoholism	35 (34.3%)
Obesity	28 (27.4%)
Vegetarian diet	26 (25.4%)
Non-vegetarian diet	76 (74.6%)
Family history	6 (5.9%)
History of Migraine	5 (4.9%)
25-hydroxyvitamin D deficiency	57 (55.8%)
MRI lesions	
Cerebellum	58 (56.8%)
Brain stem	62 (60.7%)
Basal ganglia	65 (63.7%)
Spinal cord	68 (66.6%)
Optic nerves involvement	70 (68.6%)
Mean EDSS score	3.31 ± 1.2
Subtypes	
RRMS	68 (66.6%)
SPMS	5 (4.9%)
CIS	29 (28.4%)

Table 2: Expanded Disability Status Scale (EDSS).

Parameters	Low EDSS (≤ 3) (n=56)	High EDSS (≥ 3.5) (n=46)	p value
Women	25 (45%)	35 (76%)	=0.002
≤40 years age group	34 (60.7%)	15 (32.6%)	=0.001
>40 years age group	22 (39%)	31 (67.3%)	=0.005
Hypertension	13 (23.2%)	9 (19.5%)	0.1
Diabetes Mellitus	10 (17.8%)	11 (23.9%)	0.1
Smoking	14 (25%)	23 (50%)	=0.01
Alcoholism	12 (21.4%)	21 (45.6%)	=0.01
Obesity	8 (14.2%)	20 (43.4%)	=0.002
Vitamin D_3 deficiency	22 (39.2%)	34 (73.9%)	=0.001
Family history	3 (5.3%)	3 (6.5%)	0.8
vegetarian diet	4 (7.1%)	22 (47.8%)	<0.0001
Subtypes			
RRMS	37 (66%)	29 (63%)	0.9
SPMS	3 (5.3%)	2 (4.3%)	0.9
CIS	14 (25%)	15 (32.6%)	0.5

Discussion

Age

In our present study, mean age at diagnosis of MS was 40.2 years, other studies have showed results varying from a younger age to older age Negreiros et al., 43 years [6], Joseph et al., 34.6 years [7], Sheshata et al., 25.6 years [8], Syal et al., 28.5 years [9], Negreiros et al., 32.2 years [6], Singhal et al., 33.3 years [10], and Alsaedi et al., 29.2 years [11].

Age and disability

In the current study, mean EDSS was 3.31 ±1.2 and 55% of our patients had milder disease disability (≤3.0 EDSS), these finding advocated by A1Jumah et al. [12]. Age >40 years was associated with a more severe disability compared to younger patients, these findings were supported by others [13]. However, Minden et al., showed in his study no significant association between younger age and EDSS <3.0 [14].

Gender

MS worldwide has been shown to be more common in women [6,7,10]. In the current study too, we noted higher percentage of women (60 (58.2%)) among MS patients. MS prevalence is higher in women from the onset of puberty till menarche and a complex interplay of various factors seem to be responsible, although clear impact of individual hormones have not been demonstrated. Estrogen seems to have an impact on immune system as well as CNS development [15,16]. The beneficial effect of higher levels of estrogen is noted during pregnancy when the risk of MS comes down, although usage of estrogen does not seem to improve MS or reduce relapses [4,15]. On the other hand testosterone seems to have a beneficial effect on MS prevention and the increased prevalence in men in older ages is thought to be secondary to the age related decline in testosterone levels [16].

Clinical symptoms

In the present study, 65% of MS patients presented with single symptoms; these finding were advocated by Shehata et al., (81.1% had single symptom) [8]. In the current study, optic neuritis was noted in 68.6% while ataxia was seen in 56.8% and paraesthesias in 27.4%. In imaging, we noted involvement of cerebellum in 56.8%, brain stem in 60.7%, basal ganglia in 63.7% and spinal card in 66.6%, our findings were supported by others [2,9,11]. The involvement is similar to other series on MS worldwide.

Risk factors

MS is caused by the immune system affecting healthy nerve cells, but the exact reasons for the development of the disease are not clearly understood. Complex interaction of environmental and other factors such as genetics, vitamin D deficiency, migraine, and stress seem to contribute to the risk of developing MS.

Hypertension

In the present study, we found 12.7% of patients with MS had hypertension; studies have shown similar findings [2,7] however, few studies have showed signification association between hypertension and MS [17].

Diabetes Mellitus

Prevalence of diabetes mellitus in our MS cohort was 17.6%, similar findings have been noted by others [7]. The relationship between diabetes mellitus and MS has been controversial. Many studies similar to ours showed no correlation. A study by Nielsen et al., claimed that patients with Type 1 diabetes were at more than a threefold increased risk for the development of MS [18]. Whereas Abbasi et al., reported that diabetes mellitus appeared to be related with a decreased risk of MS [19]. These effects of diabetes and hypertension on MS seem to differ from region to region and underlying genetic and behavioural factors may be the cause for these disparities.

Smoking

Recent studies have incriminated smoking as one risk factor for MS [20]. In our study, 37.2% of MS patients smoked, others have shown similar results, Wu et al., 61% [21], Kahraman et al., 34.1% [20], and Halawani et al., 53.8% [22].

Smokers have been found to have higher EDSS and Multiple Sclerosis Severity Score (MSSS) scores than non-smokers [21]. Taan et al., showed in his study association with smoking and MS [2]. In our study we found significant association between smoking and high EDSS score (<0.0001), our finding was advocated by others [20,21]. Smoking increase nitric oxide and oligodendrocytes are sensitive to nitric oxide exposure. Therefore, any exposure to nitric oxide will ultimately lead to cell death by either apoptosis or necrosis. This study supports the notion that the nitric oxide in cigarettes may be causing degeneration, demyelination, and oligodendrocytes necrosis [2].

Alcoholism

Data regarding alcoholism as a risk factor for MS is varied with some studies showing a clear association [23], in the present study, 34.3% had alcoholism, and few studies have found higher prevalence up to 52.1% [24]. Studies have showed the both genetic and environmental factors with alcohol consumption play vital role for risk of MS [25]. However, a recent study showed that alcohol consumption lead to a lower risk of MS; never drinkers were roughly 20% more likely to develop the disease [26]. We found alcohol consumption had a significant association with higher EDSS ($p<0.0001$).

Obesity

The present study we noted 27.4% with MS were obese and obesity had significant association with higher EDSS. Alsaedi et al. showed in his study normal patient having less EDSS compared to obese patients [11]. However, few studies have demonstrated no evidence between obesity and higher EDSS [27].

Food Habits

In the present study, 21.7% patients were vegetarians [7], Malli et al. reported that vegetarian diet was a significant risk factor for MS

[28]. In our study we found vegetarian diet was associated with significantly higher EDSS compared to non-vegetarian diet.

Vitamin D

Vitamin D plays a major role in neurological disorders with a recent emphasis on MS patients [29]. In our study 55.8% had 25-hydroxyvitamin D deficiency, similar prevalence has been seen worldwide [7]. Pandit et al. reported that vitamin D levels were significantly lower among MS patients [30]. Low serum 25-hydroxyvitamin D levels exert detrimental effects on MS development, which has been found in previous studies [1] and verified in the present study. Vitamin D is well-known to have many immunoregulatory elements and substantially interferes with a wide range of autoimmune diseases. Goldsmith [31] suggested that vitamin D may serve as an endogenous brake to inflammation. A study by Waschbisch et al. [32] also demonstrated how vitamin D induces the expression of the inhibitory receptor ILT- 3, which controls the T cell activation that is essential to prevent autoimmunity. Thus, it is suggested that vitamin D cotreatment with IFN beta could contribute beneficial effects to the management of the disease.

In our study, lower serum levels of vitamin D was found to be associated with higher MS disability. Thus, Vitamin D deficiency seems to not only increase the risk of MS but also seems to contribute to a more severe disability. Vitamin D deficiency may be attributed to the overall low daylight exposure in our group. This observation is also supported by other studies [16], which showed that decreased UVB exposure correlates with an increased incidence of MS [2].

Family History

The present study demonstrated family history in 5.9%, other studies have shown similar results [2,7]. Although there has been no single gene associated with MS, there has been forays into identifying susceptibility with most association discussed with HLA locus.

Migraine

We noted 4.9 % patients with MS had migraine; this is advocated by others [33]. Migraine may act as a risk factor for MS in some cases, while in other cases, MS itself could be the cause of migraine. It may also be possible that the two diseases just happen to coexist with one another. La Mantia et al., suggested that headaches were associated with the usage of IFN beta as a treatment for MS [34]. Due to this uncertainty, we encourage other researchers to assess this relationship to come to a better understanding of both MS and migraine [2].

Subtypes

Majority of patients in this study (66.6%) had RRMS, 4.9% had SPMS and 28.4% had CIS. Other studies had varied prevalence [2,7,8]. There was no association with the subtype and severity of the disease.

This may be due to the fact that the patients were enrolled during the period of relapse and not during follow up. This is a major limitation of our study that we did not have long term follow up and the impact of various parameters on chronic disability was not studied.

Therapeutic Management

The most common drugs patients were receiving prior to enrolment in this study were Avonex (interferon beta-1a) in 47% and methyl prednisolone in 37.2%. Steroids are the most common and ideal drugs in treating relapses and have been given in higher percentages for treatment disabling relapses like motor system disabilities, optic neuritis and acute ataxia [35], and inhibit pro-inflammatory cytokines and apoptosis of T cells [36] Dimethyl fumurate, teriflunamide were given to 26.8% and 25.4% respectively while less than 10% had received Betaseron (interferon beta-1b), natalizuab or other drugs like rituximab, ocrelizumab etc.

Conclusions

In our study we established female prevalence to be higher in MS patients. Age>40 years, smoking, alcoholism, obesity, 25-hydroxy vitamin D deficiency and vegetarian diet were significantly higher among patients with higher EDSS, these findings need to be confirmed by large scale studies.

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