Mycoplasma Pneumonia Seroposivity in Iranian Patients with Relapsing-Remitting Multipl Sclerosis: A Randomized Case-Control Study

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Abstract

Objectives: Environmental factors, such as different infections, have proposed to be involved in the pathogenesis of multiple sclerosis (MS). This study aimed to the evaluate mycoplasma pneumonia seropositivity, as a common cause of community-acquired pneumonia in patients with relapsing-remitting multiple sclerosis (RRMS).

Methodology: Using ELISA method, IgM and IgG antibodies to Mycoplasma pneumoniae were determined in 130 patients with relapsing-remitting multiple sclerosis (85 Remitted and 45 Relapsed) and 50 sex- and age-matched controls. The groups were compared using Kruskal-Wallis test at the significant level of $p < 0.05$.

Results: The median [interquartile range] titer of IgG in remitted multiple sclerosis group was 65.3[51.1-75.2] RU/ml versus 64[52.6-71.4] RU/ml in relapsed group and 57.5[29.2-74.3] RU/ml in control group ($p = 0.442$). There was not any significant difference between the groups base on median titer of IgM too ($p = 0.446$). The median [interquartile range] titer of Mycoplasma pneumoniae (MPn) IgG in women was 69.2[56.4-77.4] RU/ml in remitted patients versus 63.85[52.45-71.25] RU/ml in relapsed patients and 55.2[29.17-72.75] RU/ml in controls ($p = 0.022$). Post hoc analysis demonstrated significant difference between remitted patients and controls ($p = 0.002$). There was not any significant difference between men in the groups ($p = 0.7$).

Conclusions: Mycoplasma seroposivity in relapsing-remitting multiple sclerosis was not significantly different in various phases of activity of disease compare to controls; but in women, seroposivity of Mycoplasma antibodies were more than controls.

Keywords: Relapsing-remitting multiple sclerosis, Mycoplasma pneumonia, ELISA (JPMA 62: S-6; 2012).

Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS). Although MS etiology is unknown, but recent studies have suggested that autoimmune and environmental factors have important roles in its pathogenesis;[1] chronic infections such as Epstein bar virus (EBV), Human herpesvirus-6 and Human herpesvirus-7 have been proposed to have role in MS occurrence.[2-4]

The importance of infection, as a risk factor of MS, is supported by abnormal immunological factors found in spinal fluid; although no agent is consistently associated with the disease.[5] Therefore, investigating the role of different chronic infection in MS pathogenesis is reasonable.

Mycoplasma pneumoniae (MPn), which is common cause of community-acquired pneumonia,[6] trend to induce numerous CNS manifestations such as encephalitis, aseptic meningitis, polyradiculitis, cerebellar ataxia, and myeliti.[6-8] Neurologic manifestations are the most common nonpulmonary manifestations of MPn infection[9] and up to 7% of patients hospitalized with MPn may have CNS symptoms too.[6]

The mechanism of CNS involvement by MPn remains unclear and direct invasion, neurotoxin production, or an immune-mediated mechanism has been proposed.[6] It is showed that in many patients, CSF IgM and IgG markedly exceeded the corresponding serum values[10,11] that may be supported by immune mediated response.

Complement-fixing antibodies against MPn are detected in serum and cerebrospinal fluid of patients with MS and the potentially role of MPn in MS pathogenesis is suggested.[11] Acute disseminated encephalomyelitis, optic neuritis, myelitis and neuromyelitis optica[12] are reported to be associated with MPn infection[13-15] so MPn may have a possible role in development of demyelinative disease.

This study was done to evaluate MPn seroposivity in patients with MS.

Methodology

This case-control study was conducted in Isfahan, one large province in central of Iran, situated between latitudes 30 and 34 degree East. People living in Isfahan are ethnically Persian belonging to Caucasian ethnicity. The total number of patients suffering from MS in Isfahan was 1391 with prevalence of 35.5 per 100000 in year 2006.[16]

130 definite patients with MS and 50 sex and age healthy matched controls enrolled in this study.

Patients with MS (85 Remitted and 45 Relapsed) randomly allocated from Kashani MS clinic. Randomization of patients was done according to a preexisting list produced by a computer program. Diagnosis of MS was confirmed base on McDonald criteria.

After taking an informed written consent, conforming to the current revision of the Declaration of Helsinki, the baseline data were collected by a researcher-made questionnaire. In both groups, 7 cc blood was taken from each person and serum samples were freeze in -20ºC after centrifugation.

Using enzyme linked immunosorbent assay (ELISA), (EUROIMMUN, Germany) antibodies seroposivity and titers were determined in both groups.

MPn IgM titer $\geq$ 1.1 RU/ml and MPn IgG titer $\geq$ 22 RU/ml were regarded as seropositive according to laboratory kit.

The demographic data were analyzed by t-test and MPn antibodies level (including IgM and IgG) were compared in three groups by Kruskal-Wallis test. P-value < 0.05 was considered significant.

Results

A total of 130 patients with MS (107 women and 23 men) and 50 controls (38 women and 12 men) were included in this study (p > 0.05). 85 patients were in remission and 45 were in relapsed phase. Female/male ratio was 4.6/1 in patients and 3.1/1 in controls. Mean age was 30.5 years in patients and 35.6 years in control group.

Common presenting symptoms were optic neuritis, sensory symptoms, and motor signs, respectively.

The mean number of attacks per year was 1.31, and mean expanded disability status scale (EDSS) was 2.1.

The median titer of IgG (p = 0.442) and IgM (p = 0.446) were not significantly different between remitted, relapsed, and control groups (Table-1).

Table-2 shows the analysis of data based on gender; there was a significant difference in median titer of MPn IgG between women in the groups (p = 0.022). Post hoc analysis demonstrated significant difference between women in remitted and control groups too (p = 0.002).

The median titer of MPn IgM showed no significant difference between women in the groups (p = 0.7).

Also, the median titer of MPn IgG (p = 0.12) and MPn IgM (p = 0.216) were not significantly different between men in remitted, relapsed, and control groups.

Table-1: Mycoplasma pneumoniae (MPn) antibodies levels in different studied groups.

Characteristics	Groups			P-value
	Remitting group (n = 85)	Relapse Group (n = 45)	Control (n = 50)	
MPn IgG	65.3[51.1-75.2]	64.0[52.6-71.4]	57.5[29.2-74.3]	0.442
MPn IgM	0.2[0.1-0.2]	0.2[0.1-0.31]	0.2[0.1-0.2]	0.446

Data are presented as Median [interquartile range (IQR)].
P-values calculated with Kruskal-Wallis test.

Table-2: The results of comparing Mycoplasma pneumoniae (MPn) antibodies in different groups based on gender.

Characteristics		Groups			P-value	Post-hoc comparison
		Remitting group (n = 85)	Relapse Group (n = 45)	Control (n = 50)		
Women	Number	67	40	38		Rem-cont
	MPn IgG	69.2 [56.4-77.4]	63.85 [52.45-71.25]	55.2 [29.17-72.75]	0.022	(p=0.002)
	Number	67	40	38	0.7	----
	MPn IgM	0.2 [0.1-0.2]	0.2 [0.1-0.32]	0.2 [0.1-0.2]		
Men	Number	18	5	12	0.12	----
	Myco IgG	29 [18.4-64.1]	70.6 [32.25-72.25]	66.65 [27.2-80.6]		
	Number	18	5	12	0.216	----
	MPn IgM	0.2 [0.1-0.4]	0.2 [0.1-0.2]	0.2 [0.1-0.2]		

Data are presented as Median [interquartile range (IQR)].
P-values calculated with Kruskal-Wallis test.
Pairwise comparison of subgroups (Post-hoc comparison) according to Bonferroni.

Discussion

Multiple sclerosis is a chronic demyelinative disease of CNS which infections may increase susceptibility to develop it.[1]

More recently serology and polymerase chain reaction (PCR) tests have proved the importance role of Mycoplasma species in neurological disease.[17] Some researchers have described prolonged cerebrospinal fluid synthesis of IgM and IgG or detection of MPn DNA in patients with neurological complication of acute MPn infection.[8,18] MPn potential pathogenic role in MS development has suggested by presenting Complement-fixing antibodies against MPn in serum and cerebrospinal fluid of patients with MS.[11] On the other hand, there are some reports of central and peripheral nerve demyelination due to MPn infection.[19,20] In other word, atypical immune reactions in MPn infections[21] suggest a possible correlation between MPn and MS .

In spite of these findings, some researchers have not found trace of Mycoplasma and other bacterial DNA in the CSF samples of patients with MS with progressive diseases or patients in remission.[22] Similarly Casserly et al. did not detect Mycoplasma-specific nucleic acid sequences in brain, blood and CSF of patients with MS.[23]

In our regard, more than 50% of all studied patients with MS and control individuals showed serological evidence of prior infection with MPn. Based on the results of present study, there was not any significant difference between MPn antibodies in patients with MS and controls; but in women, MPn IgG was significantly higher in patients with MS than controls. Therefore, chronic MPn infection may have a possible role in development of MS among women. This finding may be related to immune response differences between men and women.

MS is more common in women rather than men. It is an autoimmune disease and different environmental factors, such as infections, can make the immunity responses that have an essential role in MS.

Non-human studies showed lifelong asymptomatic infection may create potentially autoreactive memory T-cells. This kind of T-cells will be reactivated after being exposed to the antigen released from central nervous injury and they cause autoimmune neurologic disease.[24] As it has been considered, cell-mediated responses and some autoimmune diseases are higher in women compared to men,[25] therefore, immunity response to various infections may differ according to the gender. This could explain the higher MPn IgG seropositivity in women with MS and could be suggested MPn, as an important factor in MS development.

Conclusion

Although mycoplasma seroposivity in patients with relapsing-remitting multiple sclerosis (RRMS) was not significantly different in various phases of disease activity compare to controls, but higher MPn IgG seroposivity in female gender compare to control may suggest a possible role of it in women; more studies are needed to evaluate important of this finding.

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