The Clinical Outcomes of Familial Multiple Sclerosis Patients

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Abstract

Introduction: Multiple Sclerosis (MS) is a chronic demyelinating central nervous system disease. MS is the most common neurological disease among young adolescents. Diagnosis is achieved with diagnostic criteria. Most cases of MS are sporadic, but about 20 percent of them are familial.

Materials and Methods: 363 familial and 3053 sporadic MS patients, who were followed up in Trabzon Karadeniz Technical University, Faculty of Medicine, Neurology Clinic, MS Outpatient Clinic and Samsun on DokuzMayÄ University, Faculty of Medicine, Neurology Clinic, MS Outpatient Clinic and were registered in the MS database, were retrospectively analyzed.

Results: A total of 3416 MS patients were included in the study. 363 of these patients were familial and 3053 were sporadic MS patients. Our familial MS prevalence was 10.6%.

Discussion: Our familial MS rate is 10.6%, which is consistent with current MS studies. Looking at the literature, our low prevalence rate compared to some studies might be a result of our high patient count and genetic polymorphism.

Conclusion: In familial MS cases, it is believed that the disease starts at an earlier age, the progression is faster, and the rate of conversion to secondary progressive MS is again higher and in a shorter time.

Keywords: Demyelinating disorder • Multiple sclerosis

Introduction

Multiple sclerosis is a chronic demyelinating central nervous system disease. MS is the most common neurological disease among young adolescents. Diagnosis is achieved with diagnostic criteria [1,2]. Patients may present with double vision, loss of vision in one eye, muscle weakness, sensory symptoms, and coordination disorders [3-5]. Due to the progressive damage to the nervous system, patients can become disabled and frail. Their mobility is impaired, and they need constant care [3]. Most cases of MS are sporadic, but about 20% of them are familial [4]. The etiology of MS is generally unknown, but genetic predisposition has been emphasized based on studies [6-10]. Based on twin studies, the concordance rate is 25%-30% for monozygotic twins and 3%-5% for dizygotic twins [9]. In another study, familial MS (FMS) rate was reported as 12.5% [11]. In some MS cohorts, the familial rate was reported as 20%, but in these studies, relatives with MS were defined as familial as grade 1 to 3 [12,13]. There is an approximately 0.2% risk of MS in the general population. First-degree relatives carry a relative risk of 3%-5%, a risk that is 15-25 times higher than the normal population [14]. Considering familial cases, especially in 1st and 2nd degree relatives, the excess burden of disease increases the overall risk. However, this risk was found the lowest between father-son and mother-son [15]. The effect of heredity on disease progression and severity is still unclear. Although it is said that the age of onset and the course of the disease are similar in sporadic and familial patients, it has been emphasized in some studies that familial predisposition increases the progression of the disease but does not influence the severity of the disease [16]. Again, in some studies, it has been reported that the age of onset of MS disease is earlier [17,18]. Our aim in this study is to compare the disease course and severity of familial and sporadic MS patients.

Materials and Methods

363 familial and 3053 sporadic MS patients, who were followed up in Trabzon Karadeniz Technical University, Faculty of Medicine, Neurology Clinic, MS Outpatient Clinic and Samsun on DokuzMayıs University, Faculty of Medicine, Neurology Clinic, MS Outpatient Clinic and were registered in the MS database, were retrospectively analyzed. Patients diagnosed with MS with McDonald criteria were included in the study. Patients with an unclear diagnosis of MS and patients without regular follow-up were excluded from the study. In this study, demographic data such as age, gender, age of onset, MS disability scale (EDSS) progressions, conversion times of EDSS progression from (3-6) survival times and conversion times and rates to secondary progressive MS were investigated. Necessary permission was taken from trabzon technical university ethics committee. Consent form was obtained from the patients.

Statistical data analysis

Analysis of the collected data was performed using the statistical package SPSS version 25.0. Mean values in the population were distributed based on Gauss (tested using Shapiro-Wilk test) and compared using the Student-T test. Quantitative variables that did not meet normality were compared using Mann-Whitney U test. Chi-Square Test of Independence is used for statistical analysis of qualitative characteristics. For control of Type I error, the level of significance was chosen as a=0.05. P values less than 0.05 (p<a) were accepted. The survival of familial and sporadic MS patients from the beginning were estimated using Kaplan-Meier product limit estimator and the survival distribution equality was tasted using log-rank (Mantel-Cox test). The correlation of common variables with MS death rate was analyzed using Cox proportional-hazards model. The analysis provided estimates of concurrent adjusted risk factor effects. In this study, Cox proportional analysis examined five covariables: (1) gender, (2) age of onset of MS, (3) symptoms of onset, (4) course of MS, and (5) family history of MS (more than one affected in one family, yes or no).

Results

A total of 3416 MS patients were included in the study. 363 of these patients were familial and 3053 were sporadic MS patients. Our familial MS prevalence was 10.6%. Demographic and disease characteristics of the patients are presented in Table 1. There was no statistically significant difference between the sporadic and familial MS groups in terms of age and gender characteristics. The kinship relations of familial MS patients were examined and following ratios were found: Sister (17.8%), cousin (11.1%), brother (7.6%), mother (5.7%), father (4.5%), aunt (2.2%), son and daughter (1.6%), and dizygotic twins (1.0%) (Table 2). Although the age of onset was 2 years earlier in familial MS patients, this was found to be not statistically significant (p=0.036). EDSS progression rates were found to be significantly faster in familial MS patients (p ≤ 0.001). The conversion times of EDSS scores to 3.0, 4.0, 6.0 are significantly shorter in familial MS patients compared to the sporadic group (p ≤ 0.001). The conversion rate to secondary progressive MS was higher in familial cases (p=0.016). Life expectancy in men was found to be lower compared to women (Figure 1). It was observed that the female patients with familial MS had the longest life expectancy among the groups. The shortest life expectancy, on the other hand, was found in male patients with familial MS (Figure 1). When the genders are evaluated separately based on their life expectancy, familial MS was found to have a negative effect, however it was not statistically significant. Again, the conversion time to secondary progressive MS was found to be significantly faster in familial MS patients (p ≤ 0.001). It was found that the onset of disease modifying therapies between two groups showed no significant difference (p=0.941).

Table 1. Demographic characteristics, disease distribution and progression.

Factor	Familial (n=363)	Sporadic (n=3053)	p
Gender	Male:108 (29.7%)	Male: 915 (29.9%)	0.997
	Female: 255(70.3%)	Female: 2138(70.1%)	-t
Age of onset	28.83 ± 9.38	30.05 ± 10.42	0.036
Age	41.26 ± 11.82	40.48 ± 11.86	0.281
MS course	RRMS: 250(68.9%)	RRMS: 2183(71.5%)	0.042
	SPMS: 83(22.9 %)	SPMS: 620(20.3%)	0.036
	PPMS: 30(8.2%)	PPMS: 250(8.84%)	0.912
EDSS progression rates	2.96 ± 21.05	22.97 ± 63.06	<0.001
EDSS 3 conversion time	1.21 ± 17	15.33 ± 52.55	<0.001
EDSS 4 conversion time	4.87 ± 30.15	23.03 ± 64.1	<0.001
EDSS 6 conversion time	5.73 ± 25.15	14.25 ± 56.34	<0.001
Secondary progressive MS conversion time	4.69 ± 30.09	25.69 ± 68.46	<0.001

Table 2. The kinship of familial MS patients.

Relation	n	%
Sister	65	17.9
Cousin	45	12.3
Brother	24	7.6
Mother	18	5.7
Father	14	4.5
Aunt	7	2.2
Daughter	5	1.6
Son	5	1.6
Dizygotic twins	3	1
Others	177	48.8
Total	363	100

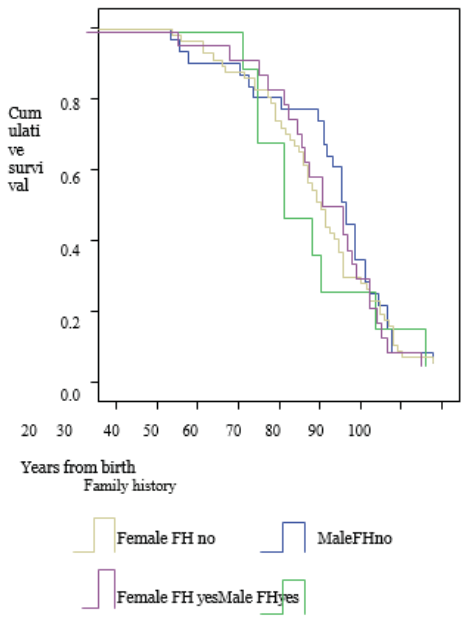

Figure 1. Survival in familial multiple sclerosis. Percentage survival by years after onset by gender and comparing different levels of familial and sporadic groups. Log-rank (Mantel-Cox) test, p=0.000.

Discussion

Our familial MS rate is 10.6%, which is consistent with current MS studies [19,20]. Looking at the literature, our low prevalence rate compared to some studies might be a result of our high patient count and genetic polymorphism. In a study conducted by the Argentina group, the prevalence rate was reported as 7.3%. In another study, the prevalence of familial MS was found to be 3%-20%, around an average of 11% [21]. In a study conducted by Nielsen, et al., it was reported that the risk of developing MS disease is 7 times higher in those with a positive family history [22]. In another study conducted by Carton, et al., it was observed that the risk of developing MS increased 10-12 times in families whose first-degree relatives were diagnosed with MS [23]. In the study conducted by the Jordan group, familial MS prevalence was found to be 9.4% [24]. The familial MS prevalence was reported to be 5%-10% by the Hungarian group whereas the Canadian group reported it to be 17.3% [25,26]. When the conducted studies are examined, it is observed that there is a difference in prevalence values among the study groups. We thought that this might be due to the fact that some studies were conducted in small populations, or it might be due to the environmental factors, geographical location and genetic characteristics that are thought to be responsible in the pathogenesis of the disease. When kinship relations were examined, we found that sister dominance in our study was consistent with the literature [15]. In a study, it was reported that the variability and effect of different factors on survival outcomes between men and women were not clearly defined [27]. In the same study, it was emphasized that female gender has a positive effect on prognosis due to early onset age. We also think that the better survival time of female familial MS patients compared to the other groups are due to these positive prognostic factors. The Saskatoon study examined five co-variable factors, including early age of onset, female gender, relapsing-remitting course of disease, late-onset disease, and progressive disease [26]. They reported that there was a strong correlation between the age of onset and the course of the disease (RR) [26]. Again, in the same study, they found that when familial factors were added to determine the effect on survival, survival time was found to be higher in female patients with familial MS [26]. Cox analysis was used to evaluate the common effect of all co-variables, and in line with our study, it showed that the presence of a family history of MS has a negative impact on the more progressive course of MS and the survival of cases with MS onset at a later age [26].

Conclusion

In familial MS cases, it is thought that the disease starts at an earlier age, the progression is faster, and the rate of conversion to secondary progressive MS is again higher and in a shorter time. Studies did so far also support this. Looking at our study, the results we obtained were consistent with the literature. Although various opinions have been reported on the prevalence and disease progression characteristics, further studies are needed to obtain more concrete data on the subject.

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