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Association of apolipoprotein E genotypes with prognosis in multiple sclerosis

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Abstract. – *Background:* **Although the association between apolipoprotein E (APOE) genetic polymorphisms and multiple sclerosis (MS), has been debated, the presence of the ε4 allele has been associated with an aggressive disease progression.**

Objectives: **Present study aimed to investigate whether or not the APOE allele has an impact on disease progression in patients with MS. The study investigated the presence and clinical correlations of certain APOE genotypes in patients with MS.**

Materials and Methods: **Fifty patients were enrolled in the study. APOE genotype was determined by polymerase chain reaction (PCR), the total apoE level was established using the nephelometric method. Expanded Disability Status Scale (EDSS) scores were also established. The progression index (PI) was calculated as the EDSS score/disease duration.**

Results: **The most common APOE genotype in MS patients was ε3/ε3 (82.0%). Male patients with MS were significantly more likely to have ε4, and at baseline, the disease duration was shorter, the EDSS scores were higher, the serum total ApoE levels were lower, and the PI was significantly higher. The MS onset age, clinical types, EDSS scores, and PI were not significantly correlated with ε4 allele-positive. Visual onset and sensory onset are good prognostic factors. There were no patients with visual onset and few patients with sensory onset in the ε4-positive group.**

Conclusions: **The present study established male patients with MS had a higher APOE ε4 frequency and disease severity, but were likely to have lower serum ApoE levels. An additional study is needed with a larger sample to include all genotypes.**

Key Words:

Multiple sclerosis, APOE, Genotype, Prognosis, EDSS.

Introduction

Multiple sclerosis (MS) is a disease affecting the central nervous system (CNS) of young adults, resulting in neurologic sequelae. The clinical progression of MS has a wide spectrum, ranging from a benign form, in which symptoms are rare, to the rapid progressive form, leading to severe disability[1]. Although the etiology of MS has not been clearly elucidated, it has been widely accepted that MS is a cell-mediated autoimmune disease, in which genetic and environmental factors are involved. Although the number of genes involved in MS is not known, it has been proposed that MS is a polygenic disease, and it is thought to be associated with chromosome region 19q13. The polymorphic apolipoprotein E (APOE) gene is located on chromosome 19q13. ApoE has a role in lipid transport and cholesterol homeostasis (APOE is used to describe the gene, whereas apoE is used to describe the protein). APOE has 3 different alleles (ε2, ε3, and ε4). The prevalences have been reported to be 10%, 74%, and 16% for ε2, ε3, and ε4, respectively[2]. A number of studies have reported conflicting opinions on the association between the APOE ε4 allele and faster and more severe progression of MS.

Although MS is progressive from the onset in some patients, most patients may never have relapses afterwards, while some patients may remain the same for years and some may have progressive MS. Because repair is essential after MS relapses for restoration of CNS functions, the APOE genotype may have an impact on the clinical progression of the disease.

MS has been demonstrated to be about twice as common in women as it is in men[3]. Furthermore, a number of prospective studies have asso-

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ciated gender with disease progression. While MS is observed to be primary progressive in men, MS is known to have better progression in women[4].

ApoE secretion and synthesis in the CNS is mediated mainly by astrocytes and other glial cells. The ApoE level around the lesion peaks a week after CNS damage and recedes gradually to baseline levels in 8 weeks. It has been proposed that following nerve damage, apoE acts as a ligand that mediates plasma lipoproteins in membrane biosynthesis during the remyelinazation and regeneration of axons, also demonstrating neurotrophic, antioxidant, and immunomodulating effects[2]. Experimental and clinical findings have revealed that APOE has an allele-specific effect (ε2> ε3> ε4) on repairing CNS damage[5].

The Expanded Disability Status Scale (EDSS) is used to evaluate disability in patients with MS. A number of studies have reported no correlation between APOE alleles and disability over time in EDSS-based disease severity evaluations[6,7]. Studies investigating the association between disease activity and serum/CSF apoE levels in patients with MS have reported inconsistent results. One of those studies demonstrated that while apoE levels in patients with MS were not unlike those observed in controls (88.04±7.53 mg/l vs 80.93 ± 6.39 mg/l; $p>0.05$), the CSF apoE levels were lower (5.41 ± 0.37 mg/l vs 7.18 ± 0.36 mg/l; $p<0.01$)[8].

The present study investigated APOE polymorphisms, the effects of APOE alleles on disease severity, the association between the ε4 allele and disease prognosis, and the effects of the APOE genotype on serum apoE levels in patients with confirmed MS.

Materials and Methods

Patients

Fifty patients with a disease duration >2 years presenting at the Multiple Sclerosis Outpatient Clinic were enrolled in the study. The patients had been clinically diagnosed with MS according to the McDonald et al diagnostic criteria[9]. Patients were excluded if they were observed with a clinical, radiologic, serologic, or pathologic finding associated with neoplasia, infection, vascular or non-demyelinating pro-inflammatory etiology. The patients were informed about the study and consent was obtained. The study was initiated after receiving the approval of our Ethics Committee.

Disability status scores of the patients were established by using Kurtzke EDSS in the remission period. The EDSS consists of 10 steps, each of which denotes an increase in impairment of functions. Scoring is based on points given for ambulation and ability to work in six separate systems. The progression index (PI), which is used to describe disease severity, was calculated as the EDSS score/disease duration. The clinical forms of MS were classified as relapsing remitting MS (RRMS), relapsing progressive MS (RPMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS). The patient information was collected regarding gender, age at MS onset, symptoms at onset, duration of disease, last EDSS score in the attack-free period, PI values, clinical form of MS, and serum apoE levels. The patients were classified into two groups (those with and without the APOE ε4 allele). The association between the APOE genotype and clinical and demographic data was evaluated.

Disease severity may vary in the initial stages of MS and may not be an indicator of its progression over the long term. Therefore, a total of 28 patients with a disease duration of at least 5 years were classified into 2 groups using the EDSS 6 criterion (not able to walk for 100 meters without unilateral assistance) and the 28 patients with disease duration of at least 5 years were again classified into two groups in terms of being above or below the median value of the PI values, indicating disease severity. These two groups were then evaluated in terms of being ε4 allele-positive.

Laboratory Tests

The APOE genotype was determined using an APOE mutation detection kit on a Light-Cycler with the PCR method (Roche Diagnostics, GmbH Mannheim, Germany). Serum apoE levels were established on a Beckman-Coulter device with the nephelometric method (IMAGE; Backman, CA, USA)

APOE Genotyping

The erythrocytes in full blood samples obtained from the patient and control groups were burst with hypotonic lysis solution, then centrifuged to separate leukocytes. Leukocyte pellets were suspended using sodium chloride-tris-EDTA (STE) solution. Sodium dodecyl sulphate (SDS) and proteinase K were added to ensure the hydrolysis of cell membranes and proteins.

Protein and cell residues were removed by using phenol-chloroform following an overnight incubation. DNA, after being purified, was left to settle in cold pure ethanol to obtain genomic DNA.

The APOE mutation detection kit (codons 112 and 158) was used as developed for Light-Cycler to establish the APOE genotype (Table I). By using PCR, a 265-bp fragment, including codons 112 and 158 of the APOE gene, was amplified from the human genome DNA. The amplicon genotype was determined with specific fluorophore-labeled probes through a fluorescent signal obtained after melting curve analysis following hybridization. Allele analysis was then performed using data analysis values to determine the allele types of the patients.

Statistical Analysis

Analysis of the data was performed using Epi Info 2000 software (CDC, Atlanta, GA, USA). A Student's t-test was used to evaluate the differences between means and chi-square analysis was used to compare frequencies. A p value <0.05 was regarded as statistically significant.

Results

Of the 50 patients enrolled in the study, 33 were women and 17 were men. The mean age of the patients was 32.9±9.8 years. The mean EDSS score of the patients in the remission period was 2.23±2.32. The mean PI value of the 50 patients after a minimum disease duration of 2 years was 0.30±0.30, and the disease severity was established to be mild. The mean serum apoE level of the patients during the remission period was 52.29±12.5 mg/L (normal, 23-63 mg/L). The APOE genotype distribution for ε3/ε3 ε3/ε4, and ε2/ε3 was 82.0%, 12.0%, and 6.0%, respectively. No patient was observed with homozygote ε2 or ε4 alleles. Similarly, none of the patients were noted with the ε2/ε2 allele. The clinical and demographic data, along with the APOE genotype distribution, are given in Table II.

Table I. APOE genotypes.

Codon 112 genotype	Codon 158 genotype	Allele type
TGC	TGC	ε2/ε2
TGC	CGC	ε3/ε3
CGC	CGC	ε4/ε4
TGC	CGC/TGC	ε2/ε3
CGC/TGC	CGC/TGC	ε2/ε4
CGC/TGC	CGC	ε3/ε4

Table II. Clinical and demographic characteristics, along with APOE genotypes, of the patients with MS.

Characteristics	
Gender (F/M), n/n	33/17
Age (years), mean ± SD	32.9 ± 9.8
Disease duration (years), mean ± SD	6.7 ±5.7
Age at disease onset (years), mean ± SD	26.2 ± 6.5
EDSS score, mean ± SD	2.23 ± 2.32
Progression index	0.30 ± 0.30
Serum apoE (mg/L)	52.25 ± 16.38
APOE genotype distribution n (%)	
ε3/ε3	41 (82.0)
ε3/ε4	6 (12.0)
ε2/ε3	3 (6.0)
ε2/ε2	–
ε2/ε4	–
ε4/ε4	–

Comparison of the female and male patients in terms of age at onset, disease duration, and EDSS scores revealed that although the age at onset was lower, the disease duration was shorter in male patients. Moreover, the EDSS score was higher and the serum apoE level was lower in men. However, the differences were not established to be statistically significant. On the other hand, the PI (EDSS/years) value, which demonstrates accumulated disability over time, was significantly higher in men (p=0.031). The clinical and demographic data for female and male patients are given in Table III.

The evaluation of the APOE genotype distribution with respect to gender in patients with MS revealed the homozygote ε3 allele to be the most common genotype in both groups. However, the incidence of ε4 allele positivity was significantly higher in men (p=0.007), as 5 of the 6 patients observed with the ε4 allele were men. Similarly, the ε3 ε4 genotype was significantly more common in male MS patients.

The clinical data, along with the PI and serum apoE levels of the patients in the ε4-positive and ε4-negative groups, are given in Table IV. No statistically significant differences were observed between the groups in terms of age at on-

Table III. Clinical and demographic characteristics, and APOE genotypes in patients with MS with respect to gender.

Characteristics	Females (n = 33)	Males (n = 17)	p
Age at onset (years), mean±SD	27.1 ± 6.6	24.5 ± 6.0	0.094
Disease duration (years), mean±SD	7.2 ± 6.1	5.7 ± 2.6	0.331
EDSS score, mean ± SD	2.0 ± 2.3	2.6 ± 2.3	0.336
PI (EDSS/years), mean ± SD	0.23 ± 0.2	0.43 ± 0.3	0.031
Serum apoE (mg/L), mean ± SD	52.5 ± 13.6	51.5 ± 17.5	0.766
APOE genotype distribution, n (%)			
ε3/ε3	31 (93.9)	10 (58.8)	0.007
ε3/ε4	1 (3.0)	5 (29.4)	
ε2/ε3	1 (3.0)	2 (11.8)	

set, disease duration, EDSS, PI, and serum apoE levels. However, the APOE ε4 carriers were observed to have a shorter disease duration, higher PI scores, and observed to be likely to have lower apoE levels.

The number of patients classified in terms of the clinical progression of the disease was as follows: 38 patients, RRMS (76%); 10 patients, SPMS (20%); 1 patient, PPMS (2%); and 1 patient, PRMS (2%). The analysis of the MS clinical types and ε4 allele carriers in those clinical subtypes revealed that 34 of the RRMS patients and 8 of the SPMS patients were in the ε4-negative group. Although there was only one patient each in the PPMS and PRMS groups, they were established to be in the ε4-negative group.

Table V gives the clinical and demographic data for the two most common groups. RRMS and SPMS patients were observed to be similar in terms of age at onset and disease duration. However, the EDSS score ($p<0.001$) and PI ($p=0.002$) in SPMS patients were significantly higher.

Although EDSS scores and PI values in SPMS patients were significantly higher than those observed in RRMS patients, the difference between the groups in terms of being an ε4 allele carrier, which is associated with bad prognosis, was not established to be statistically significant ($p=0.42$). The detailed data are given in Table VI.

The most common symptoms at onset in our patients were reported to be unilateral visual loss or blurred vision in 24 patients (48%), paresthesias or loss of sensation in the arms/legs, face, or another region in 14 patients (28%), disability in the arms or legs in 7 patients (14%), and vertigo or loss of balance in 5 patients (10%). Visual onset, associated with good prognosis, was not observed in the ε4-positive group. Similarly, sensory onset, also associated with a good prognosis, was observed to be less common among the ε4 allele carriers. The distribution of symptoms at onset with respect to the APOE ε4 allele presence is given in Table VII.

The 28 patients with a disease duration of at least 5 years were classified into two groups with respect to EDSS 6 criterion (unable to walk without unilateral assistance for 100 meters).and the comparison of the groups with respect to being an ε4 allele carrier revealed that 76% of the ε4-negative group and 66% of the ε4-positive group had not fulfilled EDSS 6 criterion by the end of the 5th year. The correlation between the EDSS score and being an ε4 allele carrier was not established to be significant ($p=0.74$). The detailed data are given in Table VIII.

The analysis of the PI values, which indicated accumulated disability over time, in the 28 patients with a disease duration of at least 5 years revealed that the correlation between PI and ε4

Table IV. Characteristics of the MS patients in the ε4-positive and ε4-negative groups.

	ε2/ε3 and ε3/ε3	ε3ε4	p
Gender (F/M), n/n	32/12	1/5	0.007
Age at onset (years), mean ± SD	26.36 ± 7.5	25.16 ± 7.1	0.714
Disease duration (years), mean ± SD	6.93 ± 5.4	5.16 ± 2.6	0.444
EDSS score, mean ± SD	2.21 ± 2.3	2.33 ± 2.1	0.909
PI value, mean ± SD	0.28 ± 0.3	0.44 ± 0.2	0.216
ApoE (mg/L), mean ± SD	52.70 ± 16.4	48.95 ± 16.7	0.604

Table V. Characteristics of MS patients with respect to clinical subtypes.

	RRMS mean ± SD	SPMS mean ± SD	p
Age at onset (years)	25.25 ± 7.4	30.19 ± 6.2	0.63
Disease duration (years)	5.97 ± 5.3	9.7 ± 3.6	0.43
EDSS score	1.45 ± 1.7	5.3 ± 1.6	< 0.001
PI (EDSS/years)	0.22 ± 0.26	0.6 ± 0.27	0.002

Table VI. APOE genotypes.

	Allele 1 ε2/ε3 and ε3/ε3 n (%)	Allele 2 ε3ε4 n (%)
RRMS	34 (89.5)	4 (10.5)
SPMS	8 (80.0)	2 (20.0)

$\chi^2 = 0.65$ $p = 0.42$.

Table VII. The distribution of symptoms at disease onset in APOE ε4-positive and APOE ε4-negative groups.

	ε2/ε3 and ε3/ε3 n (%)	ε3ε4 n (%)
Visual	24 (100)	–
Sensory	12 (85.7)	2 (14.3)
Motor	4 (57.1)	3 (42.9)
Vertigo/balance problems	4 (80.0)	1 (20.0)

Table VIII. The distribution of patients with a disease duration ≥5 years with respect to the EDSS score and the ε3/ε4 genotype.

	EDSS score <6 n (%)	EDSS score 6-10 n (%)
ε2/ε3,ε3/ε3	19 (76.0)	6 (24.0)
ε3/ε4	2 (66.7)	1 (33.3)

positivity was not significant (p=0.52). Of the patients, 80.0% in the ε4-negative group and 66.7% in the ε4-positive group were established to be under the mean value (0.30±0.30).

Although they were not observed to be statistically significant, serum apoE levels in patients during the remission period were noted to be lower in ε4 allele carriers. While the mean ApoE level in the ε4 allele-negative group was 52.7±16.4 mg/L, the mean ApoE level was 48.95±16.7 mg/L in the ε4 allele-positive group (p=0.604).

Discussion

Genetic factors have been increasingly cited among the factors that can have an impact on the prognosis of MS. However, the number of genes and the mechanisms involved has not been clearly elucidated[10-12]. We evaluated a total of 50 patients with MS (33 women, 66%; 17 men, 34%) in the present study investigating the effects of APOE genotypes on the prognosis of MS.

Bauer and Hanefeld[13] reported the age of onset to be between 21 and 40 years in 70% of the patients in their sample of 660. We observed the mean age of onset in our study sample to be 26.23±6.54 years. The female-to-male ratio has been reported to be approximately 2:1[1,14]. We established the ratio to be 1.9:1, which is consistent with previous reports.

The distribution of the APOE genotype was 82.0%, 12.0%, and 6.0% for ε3/ε3, ε3/ε4, and ε2/ε3, respectively. Evaluation of the APOE genotype in terms of gender demonstrated that the ε3/ε4 genotype was significantly more common in male patients (p=0.007). Previous studies[6,7,15-25] have established no correlation between the APOE ε4 allele and gender, with the exception of the study conducted by Al-Shammri et al[26], which reported a significantly higher prevalence of the APOE ε4 allele in female patients. In contrast to the existing data in the literature, significantly higher frequency of the APOE ε4 allele noted in male patients, in the current study, merits further investigation in a larger population. Male gender is among the poor prognostic factors in MS and the ε4 allele has often been associated with rapid progression of the condition. Although the number of patients with the ε4 allele in the present study was limited, the male patients had significantly higher PI values than the female patients. Furthermore, the disease duration was shorter and the EDSS score was likely to be higher at baseline.

The mean age at disease onset was calculated to be 26.2±6.5 years in the current study, with the

female patients being older at disease onset (24.5±6.0 vs. 27.1±6.6 years, p=0.094). Age at disease onset was not significantly different for the ε4-negative and ε4-positive patients (26.36±7.5 vs. 25.16±7.1 years, p=0.714). Most studies carried out to investigate this particular issue did not report a correlation between age at onset and APOE ε4 positivity[6,7,15-18,21,27-29]. The only different result was reported in a study conducted by Chapman et al[20], as they demonstrated that age at onset was lower in the ε4-positive group (n=41) when compared with the ε4-negative group (n=164). Consistent with previous findings, we did not observe a significant difference in the present study between the ε4-positive and ε4-negative groups in terms of age at onset.

While most studies investigating the association between clinical types of MS with APOE ε4 did not report a significant correlation between APOE genotypes and clinical subgroups[6,7,16,18,19,23,25,27,30], in their 66-patient sample Ballerini et al[15] observed that the ε2 allele carriers took longer to reach secondary progression when compared with those who were not ε2 carriers, and suggested that the ε2 allele had a protective role in terms of transformation into the progressive form.

Pirttilä et al[31] conducted a study with 105 patients with MS and classified their patients into RRMS, SPMS, and PPMS groups. Although they established no significant differences in terms of genotype distribution, they observed their PPMS patients to be more likely to be ε4 carriers. However, the difference was not established to be statistically significant. Pinholt et al[18] reported that ε4-positive RRMS patients had higher progression rates than the ε4-negative patients. In agreement with a number of studies in the literature, we did not establish a significant difference in this current study between RRMS and SPMS patients in terms of being ε4 carriers. However, we maintain that our results may have been affected by the limited number of progressive patients, the fact that most patients had benign progression, and that none of our patients were homozygote ε4 allele carriers.

An evaluation of the relationship between APOE ε4 carrier status and symptoms at onset revealed that while 48% of the patients had visual symptoms at onset, 28% had sensory, 14% had motor, and 10% had vertigo or balance problems. Onset with motor symptoms, regarded to be a poor prognostic factor, was noted in 4 patients in the ε4-negative group and 3 patients in the ε4-positive group. Although a limited number of patients did not allow a statistical analysis to be conducted, onset with visual symptoms, regarded to be a good prognostic factor, was not observed in the ε4-positive group. Similarly, few patients were observed with onset with sensory symptoms.

The following factors were reportedly associated with relatively good prognosis in MS: age at onset ≤35 years; monosymptomatic onset; sudden appearance of symptoms; remission of symptoms within a month or symptoms not lasting >2 months; no deficits after each exacerbation or improvement with minimal deficit; absence of extensor plantar response or cerebellar signs at onset; onset with monosymptomatic optic neuritis or sensory symptoms; and absence of motor symptoms at onset or pyramidal or cerebellar involvement at >5 years after onset[32-34]. No study has been conducted to investigate the association between symptoms at onset and APOE genotypes.

When we evaluated the relationship between being an APOE ε4 carrier and disease duration, the EDSS score, and PI value, we established that although female and male patients had a similar mean disease duration in the current study (p=0.331), male patients were more likely to have a shorter disease duration and being an ε4 allele carrier was not established to be correlated with disease duration.

The mean EDSS score of our patients was 2.23±2.32, with no significant difference between female and male patients (p=0.336). However, male patients were observed to be more likely to have higher scores. It was established that being an ε4 allele carrier was not correlated with EDSS score (p=0.218). Similarly, being ε4-positive was not correlated with reaching EDDS 6 in a disease duration of ≥5 years (p=0.74). The mean PI value was established to be 0.30±0.30, with male patients having significantly higher PI values (p=0.031). Although it was not established to be statistically significant, ε4 allele carriers were also observed with higher values. On the other hand, PI values were not significantly correlated with ε4 positivity in disease duration of ≥5 years (p=0.52).

Although conflicting reports have been published on the effects of APOE genotype on disease progression, the ε4 allele has generally been regarded as a poor prognostic factor. While several studies demonstrated the APOE ε4 allele to be associated with worse and faster progression[16-20,22,23,28,35], other investigations established no correlation between the ε4 allele and EDSS, disease severity, and progno-

sis[6,7,24,26,29,30,36-44]. Ballerini et al[15] maintained that the ε2 allele delayed the initiation of secondary progression. Disease severity and *APOE* polymorphisms were not established to be correlated in a study conducted on 408 patients with MS investigating the association between APOE genotypes (particularly ε2 and ε4 alleles) with MRI findings and disease severity[27]. Ferri et al[30] reported that the ε2-4 polymorphism was not associated with disability in MS, as evaluated by EDSS. In contrast, Evangelou et al[16] demonstrated that APOE ε4 positivity and homozygosity were associated with faster progression in EDSS. While a study associated the ε2 allele with disease severity[45], another study reported that remyelinazation in patients with MS who were ε2 allele carriers was less adequate compared to that observed in carriers of other alleles[46] On the other hand, the ε3 allele was not associated with disease severity in MS. A study with 76 RRMS patients investigating the impact of ε4 allele positivity in MS on brain atrophy reported that the incidence of brain atrophy was higher in the ε4-positive RRMS patients than the ε4-negative group and healthy controls[35]. Morphologic support regarding the detrimental effect of the ε4 allele was provided by Fazekas et al[47], who evaluated brain lesion volume on MRI and the APOE genotype in 83 patients with MS. Parmenter et al[48] reported that the ε4 allele was not significantly associated with physical disability and cognitive functions. Nevertheless, the prevalence of ε4 allele carriers was higher in the group with cognitive function impairment when compared with the group whose cognitive functions were intact (27% vs. 52%).

We did not have any homozygote ε4-positive patients in the present study and the mean EDSS score of the patients was low. Many of our patients had been undergoing immunosuppressive and/or immunomodulator therapy, which may have had an impact on prognosis. We maintain that more significant results could be obtained by increasing the number of patients as well as including homozygote ε4-positive patients.

Serum apoE levels that were established in the episode-free period in the present study had a mean value of 52.25±16.38 mg/L, with no significant differences between females and males (p=0.766). The ApoE level was 48.95±16 in the ε4-positive group, while it was 52.7±16 in the ε4-negative group (p=0.200). Although the difference was not established to be statistically significant, the ε4-positive group had lower levels.

It was established that serum apoE levels of patients with MS and other neurologic diseases were not different from those of controls in a study conducted by Gaillard et al[8] on serum and BOS apoE levels in patients with MS, Guillain-Barré syndrome (GBS), amyotrophic lateral sclerosis (ALS), and other neurologic diseases. However, the CSF apoE levels in the patients with MS were lower than those observed in the controls and the patients with other neurologic diseases. Moreover, ε4 allele carriers in all patient groups were established with lower serum apoE levels when compared with ε4 allele-negative patients, but the BOS level was not different. It was suggested that APOE polymorphisms regulated serum apoE concentrations, but had no impact on CSF levels[8]. Carlsson et al[49], Gelman et al[50], and Rifai et al[51] reported depressed serum apoE levels in MS patients during remission but no significant alterations in CSF apoE levels. However, the APOE genotype was not investigated in those studies.

Pirttilä et al[31] reported that serum and CSF apoE levels in immunosuppressive and non-β IFN receiving MS patients during remission were not associated with disease subtype, disease duration, and genotype. They also reported stable serum and CSF apoE levels in RRMS, SPMS, and PPMS patients measured at different times and concluded that they would have no value as activity markers in MS patients. Consistent with the results of the study conducted by Gaillard et al[8], APOE ε4-positive patients were observed to be more likely to have lower apoE levels in the present study as well. However, the results may have been affected by the lack of homozygote ε4 carriers in our study sample and by the fact that the patients were evaluated during the remission stage.

In conclusion, the results of this current study suggested that ε4 positivity may be associated with disease progression in MS patients. Although the difference was not statistically significant, PI values were noted to be higher in the ε4-positive group, while no significant differences were observed between the APOE ε4-positive and APOE ε4-negative patient groups in terms of age at onset, disease duration, clinical types of MS, and EDSS scores. Furthermore, there were no patients with visual onset and few patients with sensory onset in the ε4-positive group. The patients in the ε4-positive group were also observed to be more likely to have lower serum apoE levels. However, it was concluded that further studies with larger study samples would yield more statistically significant results.

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