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Title: The Possible Relationship Between the APOE4 Isoform and White Matter Loss in Multiple Sclerosis Patients: An Exploratory Study

Running Title: APOE4 and White Matter Loss

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To appear in: **Basic and Clinical Neuroscience**

Received date: 2026/01/31

Revised date: 2026/05/27

Accepted date: 2026/06/06

Please cite this article as:

Maghbooli, Z., Negah, S.S., Sahraian, M.A. (In Press). The Possible Relationship Between the APOE4 Isoform and White Matter Loss in Multiple Sclerosis Patients: An Exploratory Study. Basic and Clinical Neuroscience. Just Accepted publication Jul. 10, 2026. Doi: http://dx.doi.org/10.32598/bcn.2026.8523.1

DOI: http://dx.doi.org/10.32598/bcn.2026.8523.1

Abstract:

Background: Apolipoprotein E (APOE) is crucial for neuronal maintenance and myelin repair. The APOE4 isoform is associated with an increased risk of neurodegeneration in multiple sclerosis patients. This study investigated the association between APOE polymorphisms and brain atrophy in multiple sclerosis patients.

Methods: The current cross-sectional study was performed on 70 relapsing-remitting multiple sclerosis (RRMS) patients, evaluating two common missense APOE polymorphisms, rs429358 and rs7412, in all participants. The FreeSurfer software measured whole-brain volume by analyzing T1-weighted Magnetic Resonance Imaging (MRI) sequences.

Diffusion tensor imaging (DTI) data were preprocessed with MRtrix3 and analyzed using FSL.

Results: Patients with APOE4 exhibited lower white matter (WM) volume than those without this isoform (274.25±32.20, vs. 307.51±36.36, p=0.02). After adjusting for confounding factors, there was a significant association between APOE4 and lower WM volume (p=0.03, partial Eta square (η^2) = 0.08). Indeed, a negative independent association was found between disease duration and WM volume (p = 0.02, η^2 = 0.09).

DTI data were analyzed in 7 APOE4 carriers and 8 non-carriers matched for age, sex, and MS duration. FA in WM (1.75(0.13), vs. 1.83 (0.18)) and corpus callosum (2.09(0.78), vs. 2.21(0.30)) were lower in APOE4 carriers, but not significantly (p>0.05).

Conclusion: The present study suggested a potential genetic influence of APOE4 on brain WM atrophy, specifically the corpus callosum, in MS patients.

Keywords: Multiple sclerosis, brain mapping, white matter atrophy, APOE

Background

Multiple sclerosis (MS) is a progressive neurologic disorder of young adults, affecting around 2.8 million people worldwide (Walton et al., 2020). It is characterized by an immune attack on the myelin sheath surrounding nerve fibers in the central nervous system (CNS), resulting in extensive damage to both white matter (WM) and gray matter (GM) in the brain and spinal cord (Lie et al., 2022). The underlying mechanism of MS pathogenesis involves an impaired immune response and the activation of inflammatory pathways, which contribute to the progression of neurodegeneration (Horáková et al., 2010). In part, this immune-inflammatory-mediated damage to the myelin destroys both WM and GM (Inglese & Petracca, 2015; Nave & Werner, 2014).

Chronic brain volume loss (BVL) is a reliable indicator of neurodegeneration in MS (Uher et al., 2021). Studies have shown that rates of BVL are already elevated in the early stages of MS and continue to increase as the disease progresses (De Stefano et al., 2014). In particular, patients with relapsing-remitting MS have annual BVL rates that are significantly higher than those of healthy individuals (Scahill et al., 2003; Simon, 2006; Takao, Hayashi, & Ohtomo, 2012). A systematic review examined the association between BVL and disability in multiple sclerosis (MS), suggesting that whole-brain atrophy correlates with greater physical disability progression in MS patients (Matthews et al., 2023). Furthermore, a ten-year follow-up study indicated a significant trend linking the decreases in WM volume to MS disability progression (Jacobsen et al., 2014). These findings highlight the accelerated neurodegeneration in MS compared to normal aging.

Genetic predisposition can influence disease progression and, consequently, the extent of brain atrophy in MS patients (Consortium*† et al., 2019). Among genetic factors, the impact of Apolipoprotein E (APOE) polymorphisms has been studied in the pathogenesis of Alzheimer's disease, where it is associated with neuronal loss leading to brain atrophy (Fernández-Calle et al., 2022).

APOE is the primary apolipoprotein of the CNS expressed by astrocytes, which are the primary cells that produce cholesterol in the CNS of adult people (Karahan, Dabin, Tate, & Kim, 2021). This cholesterol is then transported via APOE to the neurons, which are used to form cell membranes and

synapses (Karahan et al., 2021) while oligodendrocytes use cholesterol for myelin production (Saher & Stumpf, 2015). Although astrocytes are the primary source of APOE in the CNS, studies have shown that elevated levels of APOE secreted by microglia can significantly affect brain lipid homeostasis and myelin metabolism (N. Wang et al., 2022). In the inflammatory condition of MS pathogenesis, myelin abnormalities trigger microglia activation, which is responsible for cellular debris clearance from damaged myelin sheaths (Praet, Guglielmetti, Berneman, Van der Linden, & Ponsaerts, 2014; Safaiyan et al., 2016; N. Wang et al., 2022). High degradation of myelin can surpass the ability of microglia to clear debris, resulting in the buildup of fatty acids and lipid-rich materials, manifesting as lipid droplets and cholesterol crystals in lesions (Chausse, Kakimoto, & Kann, 2021; Gouna et al., 2021; Stadelmann, Timmler, Barrantes-Freer, & Simons, 2019).

APOE has three isoforms in humans: ε2, ε3, and ε4 (Utermann, 1987); each affects neurite outgrowth differently. APOE2 is associated with increased neurite growth and is considered neuroprotective, whereas APOE3 is generally considered to have a baseline role without contributing to neurite growth. The APOE4 isoform is associated with inflammation and oxidative stress in various neuropathological processes (Iannucci, Sen, & Grammas, 2021). The specific proteolysis of neurons by APOE4 leads to the production of bioactive toxic fragments, which enter the cytoplasm, modify the cytoskeleton, disturb mitochondrial energy balance, and cause cell death (S. Wang et al., 2022). Although this evidence shows that APOE4 can contribute to brain atrophy observed in neurodegenerative disorders, there is not enough evidence to show the role of APOE in brain atrophy in multiple sclerosis at a clinical grade. Therefore, this study investigated a possible association between genetic APOE variants and brain atrophy rates.

Methods

Study design and population

This cross-sectional study was conducted in the Multiple Sclerosis Research Centre of Tehran University of Medical Sciences. The participants in this study (N = 70) were MS patients referred to the MS clinic at Sina Hospital, a leading referral center for multiple sclerosis in Iran. Inclusion criteria

were: age 18–55 years, diagnosis of relapsing-remitting MS (RRMS) according to the McDonald criteria, no current pulse therapy or corticosteroid use, and no relapse within the previous 3 months. All MS patients met McDonald's criteria (Thompson et al., 2018) for diagnosis. Medical history, age at the time of MS diagnosis, Expanded Disability Status Scale (EDSS), and medications were verified in the patient's medical records and subsequently confirmed by neurological examinations.

Genotyping and phenotypes of APOE

The APOE polymorphisms in the study group were identified by first collecting whole blood samples from participants, which were then placed in EDTA-containing tubes. Genomic DNA was extracted using a phenol-chloroform protocol, followed by polymerase chain reaction (PCR) to amplify two common missense single-nucleotide polymorphisms (SNPs), rs429358 (388T>C, ASP416Glu), and rs7412 (526C>T, Thr420Lys). The PCR products were then analyzed by restriction fragment length polymorphism (RFLP) analysis to determine genotypes.

The primers for APOE gene polymorphisms were as follows: Forward, 5′-GGCACGGCTGTCCAAGGA-3′ and Reverse, 5′- GCCCCGGCCTGGTACACTGCC-3′. PCR amplification was conducted after initial denaturation at 94 ºC for 5 min, followed by 35 cycles of denaturation at 94 ºC for 25 seconds, annealing at 67 ºC for 25 seconds, and elongation at 72 ºC for 25 seconds. A final extension step was performed at 72 ºC for 10 minutes. The resulting APOE PCR products were digested with the restriction enzyme *HhaI* (Takara, Cat No 1056A) at 37 ºC for one hour. The samples were stained with SYBR Green (Cinnagen, Iran) and visualized on a 12% polyacrylamide gel. To verify the accuracy of this genotyping method, 10% of the APOE3 samples and all APOE2 and APOE4 samples were sequenced. Hardy-Weinberg equilibrium (HWE) and linkage disequilibrium (LD) tests for the SNPs were also evaluated. The three common APOE isoforms were defined as follows: ε2(388 T–526 T), ε3(388 T-526C), ε3 ε4(388C-526C). Based on these two SNPs, six genotypes can be formed: (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, and ε4/ε4) (Zannis et al., 1982).

Brain volumetric analysis and image acquisition

T1 Magnetic Resonance Imaging (MRI) was used for whole-brain volumetric analysis at the National

Brain Mapping Laboratory in Tehran, Iran. Images were acquired on a 3T Siemens Magnetom Prisma Fit Scanner with a 64-channel head and neck coil. T1-weighted anatomical images were obtained using a 3D magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence with the following parameters: repetition time (TR) of 1800 ms, echo time (TE) of 3.5 ms, inversion time (TI) of 1100 ms, flip angle of 7°, field of view (FOV) of 256 × 256 mm^2, matrix size of 256 × 256, and an isotropic voxel size of 1 × 1 × 1 mm^3. Whole-brain coverage was achieved with 160 contiguous sagittal slices. Additionally, T2-weighted FLAIR images were acquired using 3D-FAST spin-echo techniques with an isotropic voxel size of 1 × 1 × 1 mm^3, TR/TE = 3000/384 ms, and 144 continuous sagittal slices, ensuring comprehensive brain coverage.

Image processing

The structural MRI data were processed using FreeSurfer (version 7.2.0) (https://surfer.nmr.mgh.harvard.edu/).

The original DICOM files were first converted to MGZ format, after which the recon-all tool was employed for comprehensive preprocessing. This pipeline consisted of several key steps: motion correction, intensity normalization, skull stripping, automated segmentation of cortical and subcortical structures, and surface reconstruction. The recon-all process also included the creation of cortical thickness maps and the extraction of surface-based anatomical features. The default FreeSurfer pipeline also generated detailed anatomical labels based on the 'Desikan-Killiany' cortical atlas. After preprocessing, volumetric data were extracted using the asegstats2table command in FreeSurfer. This tool generates region-specific volumetric statistics, including cortical GM thickness, subcortical GM volumes, WM structures, ventricular systems, and cerebrospinal fluid (CSF).

Classification of Brain Volumetric Measures

The brain volumetric measures were classified according to anatomical regions derived from FreeSurfer's segmentation. The regions assessed include GM and WM structures and ventricles. Table 1 summarizes the anatomical regions included in each volumetric measure.

***Table 1**: Anatomical Regions Included in Brain Volumetric Measures*

Volumetric Measure	Anatomical Regions Included in the sum volume
Cortical GM	Left/right cortical gray matter
Subcortical GM	Left/right thalamus, caudate, putamen, pallidum, hippocampus, amygdala, accumbens area, ventral diencephalon
Cerebral and Cerebellar WM	Left/right cerebral WM, cerebellar WM, corpus callosum*
Ventricular Volumes	Left/right lateral ventricles, left/right inferior lateral ventricles, third and fourth ventricles, total CSF volume.
Total Brain Segmentation	Brain structures, excluding ventricles and incorporating surface measures

**(The corpus callosum was segmented into posterior, mid-posterior, central, mid-anterior, and anterior sections).*

Diffusion Tensor Imaging

Diffusion-weighted images (DWI) were acquired using a single-shot spin-echo echo-planar imaging (SE-EPI) sequence (b = 700 s/mm^2), 2 non-diffusion-weighted reference images (b = 0 s/mm^2), TR = 11000 ms, TE = 105 ms, FOV = 128 × 128, number of slices = 60, number of volumes = 32, voxel size = 2.0 × 2.0 × 2.0 mm^3. To correct for EPI distortions, a reverse phase encoding was also acquired (TR = 11000 ms, TE = 105 ms, FOV = 128 × 128, number of volumes = 5, number of slices = 60, voxel size = 2.0 × 2.0 × 2.0 mm^3).

T1-weighted (T1w) images were acquired using a 3D magnetization prepared rapid acquisition gradient-echo (MPRAGE) sequence with Inversion Time (TI) = 1,100 ms, Repetition Time (TR) = 1800 ms, Echo Time (TE) = 3.5 ms, Flip Angle = 7, Field of View (FOV) = 256 × 256, number of slices = 160, voxel size = 1.0 × 1.0 × 1.0 mm^3

Diffusion tensor imaging preprocessing

Diffusion tensor imaging (DTI) data were preprocessed using MRtrix3 and analyzed with FSL (version 6.0.6.5). The preprocessing included denoising with MP-PCA, Gibbs ringing correction, motion and eddy current correction, and susceptibility-induced distortion correction using the top-up algorithm. Indeed, bias field correction was performed to address intensity inhomogeneities.

DTI analysis using the JHU white matter atlas

To investigate diffusion metrics within standardized white matter tracts, we performed a region-of-interest (ROI) analysis using the JHU ICBM-DTI-81 white matter labels atlas. The JHU atlas, which is defined in MNI space, was non-linearly registered to each subject's native diffusion space using ANTs registration (antsRegistrationSyNQuick.sh). The fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were generated for each subject.

For each subject, the JHU atlas was transformed into diffusion space using a combination of affine and nonlinear warp fields. Following this step, binary masks were created for each of the 50 white matter ROIs by thresholding on the respective label indices. These masks were applied to the subject-specific diffusion metric maps using FSL's fslstats to extract the mean value within each region.

Statistical analysis

All the statistical analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL). Data were expressed as numbers (%) for categorical values and mean ± standard deviation for continuous variables. The volumetric data from all subjects were compiled and statistically analyzed to determine the relationship between these structural measures, clinical variables, and APOE polymorphism. Normalization of volumetric brain data was based on the estimated total Intracranial Volume (eTIV(mm^3)).

Subgroup analyses were conducted according to APOE4 carrier status. Due to the absence of APO4 carriers among men, all APOE4-related analyses were restricted to women. To further investigate DTI data, median (IQR) FA, MD, AD, and RD values in total WM and the CC were compared between 7 APOE4 carriers and 8 non-carriers, matched for relevant covariates, including age and disease duration. The raw data are provided in Supplementary File 1. Participant demographic and clinical data were collected using descriptive statistics. Data normality was tested using the Shapiro–Wilk test. The differences between study groups were compared using the Student's t-test for continuous variables and the Chi-square test for categorical variables. A univariate general linear model assessed the relationship between brain atrophy classifications and the APOE4 allele. The model accounted for potential confounders, including age, obesity, anti-CD20 therapy, and disease duration. If the p-value was less than 0.2 (p-value < 0.2), the variable was included for adjustment.

Cardiovascular risk factors (diabetes, dyslipidemia, and hypertension) were excluded from the model due to diabetes in only one subject, and no one had other cardiovascular risk factors.

Results:

Baseline and clinical characteristics:

The study population was recruited between September and December 2022 (Table 2). All participants were diagnosed with RRMS with an EDSS≤5 and had no comorbidities with other autoimmune diseases. Only one patient had a history of type 2 diabetes mellitus (T2DM). None of the patients reported dyslipidemia, hypertension, or taking related medications. None of the patients were receiving steroidal medications (such as prednisolone, dexamethasone, or other corticosteroids) within the last three months before the study. Except for three patients, all patients were on disease-modifying treatments (DMTs).

Table 2: Clinical and demographic characteristics of MS patients

Demographic features	**MS (N=70)**
Age (years)	36±7
Sex (female)	80% (56)
BMI (kg/m2)	26.5±4.2
Smoking	13%(9)
Clinical characteristics	
Disease duration (years)	7 ±5
EDSS	2(2)
Receiving anti- CD-20	43% (30)
Hypertension	-
Dyslipidemia	-
Diabetes	1

EDSS: Expanded Disability Status Scale

Polymorphisms of the APOE gene:

Table 3 presents the genotype, allele, and phenotype frequency in the MS patients. In our study population, the minor allele frequency was 0.57 for rs429358 (C allele) and 0.79 for rs7412 (T allele).

Allele frequencies for both SNPs were in Hardy-Weinberg equilibrium (p = 0.25 for rs429358, p = 0.87 for rs7412). The dominant genotype of SNP rs429358 was TT (88.6% of participants), while for rs7412, the homozygous CC genotype was the most common (85.7% of participants) (Table 3). The ε4 isoform was observed in 11.4% (ε3/ε4, or ε4/ε4) of the individuals, with no APOE4 carriers identified among the male participants.

Table 3: Genotype, allele frequency, and phenotype of the APOE gene in MS patients

Genotypes			
rs429358	N (%)	**rs7412**	N (%)
TT	62 (88.5)	CC	60 (85.7)
CC	0	TT	1 (1.4)
TC	8 (11.5)	CT	9 (12.9)
Allele freq.			
rs429358		**rs7412**	
T	0.943	C	0.921
C	0.057	T	0.079

Brain Volumetric Measures:

Volumetric measurements were categorized by anatomical region to investigate the role of the APOE4 allele in brain atrophy. Among brain volumetric measures, the cerebral and cerebellar WM volume (Left/right cerebral WM, cerebellar WM, and corpus callosum) was significantly lower in MS patients with the APOE4 allele than those without APOE4 (p=0.02). Cortical and subcortical GM were smaller in patients with the APOE4 allele than those without APOE4, but this difference was not statistically significant (p>0.05). Additionally, ventricular volumes were higher in MS patients with APOE4 compared to those without APOE4, although the difference was not statistically significant (p = 0.27).

Table 4: Comparison of brain volumetric regions of MS patients- APOE4 carriers versus non-carriers

Volumetric Measure	With **ε4 (N=8)**	Without **ε4 (N=62)**	P-value
Cortical GM	301.95±12.25	314.64±28.29	0.22
Subcortical GM	32.80±3.93	36.03±5.07	0.09
Cerebral and Cerebellar WM*	274.26±32.19	307.51±36.36	**0.02**
Ventricular Volumes	19.43±7.67	16.59±6.74	0.27
Total Brain Segmentation	698.40±36.65	744.69±6673	0.06

* Left/right cerebral WM, cerebellar WM, corpus callosum

There were no significant associations between WM and taking CD20 (p = 0.6) or obesity (p = 0.4). To address APOE4's independent role in the cerebral and cerebellar WM volume, a univariate general linear model was used to adjust for confounding factors, including age and MS duration. In our data, no men were in the APOE4 group, so men were excluded from the model. After adjusting for confounding factors, there was a significant association between APOE4 and lower WM volume (p=0.03, partial Eta square (η^2) = 0.08). Indeed, a negative independent association was found between disease duration and WM volume (p = 0.02, η^2 = 0.09).

To examine the role of APOE on gray matter, the same analysis was repeated to adjust for confounding factors. There was no significant association between the APOE4 allele and total GM (cortical and subcortical gray matter) volume (p=0.16). Only MS duration had an independent association with GM volume (p=0.01, $\eta^2=0.1$).

Regarding total GM, there was no significant difference between APOE4 carriers and non-carriers (406.43±16.26 vs. 422.73±16.26, p=0.2). Patients with long disease duration had lower GW volume (r=-0.32, p=0.006).

DTI result:

DTI data were analyzed in 8 APOE4 carriers and 8 non-carriers matched for age, sex (all women), and MS duration. FA in WM with median (IQR) 1.75(0.13), vs. 1.83 (0.18) and corpus callosum 2.09(0.78), vs. 2.21(0.30) were lower in APOE4 carriers, but not significant (p>0.05).

Discussion

Our recent study considered brain atrophy in RRMS and extended these findings by demonstrating the APOE4 phenotype. Our findings indicated that those carrying the APOE4 isotype showed more severe white matter (WM) atrophy without apparent impact on gray matter (GM). This reduction spanned cerebral and cerebellar WM structures, including the corpus callosum (CC), suggesting a possible reduced WM integrity in the presence of the APOE4 isotype.

Based on DTI data from subsamples of the study population, alterations were observed in the FA of WM and CC of APOE4 carriers. The corpus callosum, which connects the two brain hemispheres, is frequently affected by MS pathology (Garg et al., 2015). MS patients often exhibit a decrease in the size of the corpus callosum compared to healthy controls (Granberg et al., 2015). Corpus callosum atrophy in MS is associated with cognitive impairment, and atrophy patterns appear to vary with longer disease duration (Granberg et al., 2015). In this exploratory study, corpus callosum (CC) integrity, which indicates white matter damage, was lower in patients carrying the APOE4 allele than in non-carriers. However, due to the small number of APOE4 carriers, further studies are needed to validate the association between the APOE4 allele and MS progression.

The effects of APOE polymorphisms, the APOE4 allele, are important as they have been linked to neurodegeneration in neurological diseases such as Alzheimer's disease (Naseri et al., 2022). According to various studies, the APOE4 variant is associated with enhanced neuroinflammatory responses, increased oxidative stress, and impaired lipid transport factors, all of which are critical for MS pathogenesis (Parhizkar & Holtzman, 2022; Yin & Wang, 2018).

There is still a gap in the literature regarding the definitive pathophysiologic mechanisms underlying APOE4-related brain atrophy in MS patients. One possible explanation for our finding is that altered lipid transport in the APOE carriers may impair myelin repair function, thereby contributing to axonal injury and reduced white matter integrity (Cheng et al., 2022). In addition, APOE4 may contribute to neurodegenerative progression in MS by affecting the function and recruitment of glial cells, particularly astrocytes and oligodendrocytes, which are essential for lesion repair, potentially promoting a pro-inflammatory environment and delayed recovery (De Stefano et al., 2004) (De

Stefano et al., 2004). Such disruption could cause sustained inflammation and hamper healing processes, ultimately exacerbating the entire neurodegenerative process in MS.

Also, APOE4 may influence glial cell function, particularly astrocytes and oligodendrocytes, which are essential for lesion repair, potentially promoting a pro-inflammatory environment and delayed recovery (De Stefano et al., 2004). Other proposed mechanisms include APOE4-related cytoskeletal disruption and mitochondrial dysfunction, which may further compromise neuronal resilience (Brodbeck et al., 2011; Huang et al., 2001). However, further study will be needed to address the exact contribution of APOE4 to MS-related brain atrophy.

Our study found an independent association between the loss of WM and the duration of MS, suggesting that WM integrity may be more closely related to disease duration. However, longitudinal studies are needed to determine whether WM integrity is a useful marker of disease progression. In our data, an association was found between the APOE4 isoform and lower WM volume, indicating a potential genetic contribution to brain atrophy in MS.

In the case of GM volume, the disease duration was significantly associated with reductions in GM volume, whereas the GM atrophy did not depend on APOE genotype. In contrast to our finding, Horáková et al. reported that APOE 4 carriers among MS patients showed a significantly faster reduction in gray matter and whole brain volume than non-carriers over 15 years (Horáková et al., 2010). This discrepancy is likely due to the small sample of APOE4 carriers in our study population.

Although clinical symptoms often do not match the changes observed on conventional MRI measurements (Healy et al., 2017) whole-brain atrophy correlates significantly with physical disability in MS patients (Rocca, Comi, & Filippi, 2017; Rudick, Fisher, Lee, Duda, & Simon, 2000). Also, it serves as a valid and sensitive measure of the disease progression in this population (Andravizou et al., 2019). However, the brain atrophy of the RRMS patients in our study did not show any association with EDSS. This may be because our patients had an EDSS of EDSS score of 5 or less.

This study has several limitations. First, the small number of APOE4 allele carriers may limit statistical power to detect the differences in brain atrophy for WM and GM. Second, the APOE4-related association was observed only in women in our study; this finding should be interpreted

cautiously because all APOE4 carriers were women, and the result may reflect the composition of the sample rather than a true sex-specific effect. Third, the cross-sectional design limits our ability to establish the causality between APOE genotypes and potential brain atrophy. Lastly, although we controlled for several confounding factors, other environmental and genetic factors, MS treatment strategies, and the disease disability severity influences on brain atrophy may not have been accounted for in our model. Future longitudinal studies are needed to examine these associations more thoroughly and to better characterize their temporal dynamics.

Despite these limitations, this study offers valuable insights into the relationship between the APOE genotype and brain atrophy in MS patients, contributing to a better understanding of how genetic factors may influence disease progression. By focusing on a specific group of patients with RRMS, we aimed to minimize variability and increase the relevance of our findings. In addition, our use of advanced imaging techniques enabled a more precise assessment of brain atrophy compared to conventional methods. Although the differences in DTI results were not statistically significant, likely due to the small sample size of APOE4 carriers, these findings suggest a potential association with disease progression and warrant validation in longitudinal studies. Given the exploratory nature of this study and the limited sample size, these results should be considered preliminary findings that require further image processing with a larger sample size.

Conclusions

MS is a multifactorial disorder with both inflammatory and neurodegenerative pathogenesis and is also influenced by genetic background. We have found that a longer duration of MS correlates with greater brain atrophy, indicating that higher brain atrophy is linked to the chronicity of the disease and neurodegenerative changes. This confirms that brain volume loss is a critical marker of disease progression. Our results provide initial evidence that APOE polymorphisms, particularly in women, may contribute to increased brain atrophy in the white matter of MS. However, further research will be needed to address the mechanisms underlying the clinical implications of these associations.

List of abbreviations

AD: Axial Diffusivity
APOE: Apolipoprotein E
BVL: Brain Volume Loss (BVL)
CNS: Central Nervous System
DMT: Disease-Modifying Treatment
DTI: Diffusion Tensor Imaging
DWI: Diffusion-Weighted Images
eTIV: Intracranial Volume
FA: Fractional Anisotropy
GM: Gray Matter
MRI: Magnetic Resonance Imaging
MD: Mean Diffusivity
RD: Radial Diffusivity
ROI: Region-Of-Interest
RRMS: Relapsing-Remitting Multiple Sclerosis
WM: White Matter

Declaration

Ethics approval and consent to participate

This study was conducted following the Declaration of Helsinki and was approved by the Ethics Committee of the Neuroscience Institute of Tehran University of Medical Sciences (IR.TUMS.NI.REC.1402.013). Written informed consent was obtained from each participant.

Consent for publication

Not applicable

Availability of data

The datasets generated and/or analyzed during the current study are available in the European Variation Archive (https://www.ebi.ac.uk/eva/?Submit-Data) repository, with accession number # PRJEB104186.

Conflict of interest statement

The Authors have no competing interests to declare that are relevant to the content of this article. Mohammad Ali Sahraian has received educational, research grants, lecture honorarium, travel supports to attend scientific meetings from Biogen-Idec, Merck-Serono, Cinnagen, Zistdaru, Zahravi and Genzyme.

CRediT authorship contribution statement

XX: Conceptualization, Methodology, Analysis, Writing – original draft

XX: Data Validation, Writing – review & editing

XX: Supervision, Methodology, Writing – review & editing

All authors reviewed and commented on earlier versions and approved the final manuscript.

Acknowledgments

We sincerely thank the National Brain Mapping Laboratory for its generous support in providing MRI services.

This work was supported by the Multiple Sclerosis Research Center, Neuroscience Institute of Tehran University of Medical Sciences, Tehran, Iran (Grant number 64033-235-1-1402).

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