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ORIGINAL ARTICLE

The Role of Brain Derived Neurotrophic Factor Val66Met Polymorphism in Multiple Sclerosis Disability and Cognitive Impairment

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ABSTRACT

Background: Brain derived neurotrophic factor (BDNF) played a role in neuroplasticity and was involved in several autoimmune diseases including multiple sclerosis (MS). Val66Met polymorphism affects BDNF secretion and needs more research to determine its impact. This study aimed to evaluate the role of this polymorphism on motor disability and cognition in MS patients. **Methods:** This is a case control study involving 100 subjects (50 MS patients, 50 controls). A genetic testing for BDNF Val66Met and a thorough neuropsychological evaluation using the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) in the approved Arabic version were performed for all subjects. Progressive clinical disability measurements by the Expanded Disability Status Scale (EDSS) along with the Multiple Sclerosis Severity Scale (MSSS) were done for MS patients. **Results:** MS patients with the Met allele variant had longer course duration (P=0.009). Val/Val genotype patients had significantly more frequent relapses (P=0.017). Met carrier patients showed lower scores on all subtests of BICAMS but only reached a statistically significant difference in the Symbol digit modality test (SDMT) (P=0.04). In the logistic regression analysis for factors predicting disability, BDNF Val66Met polymorphism was not associated with disease disability. More frequent relapses, presence of high lesion load and cervical lesions on MRI brain could predict increasing disability on multivariate analysis.
Conclusions: MS patients having met allele of the BDNF gene had significant cognitive dysfunction on the SDMT. However, our results could not suggest a significant effect of this polymorphism on other subtests of BICAMS or on clinical disability.
Key words: Multiple Sclerosis; cognition; disability; polymorphism.

INTRODUCTION

Cognitive problems affect a large percentage of Multiple Sclerosis (MS) patients reaching up to 70% and causing a notable impairment of daily activities [1].
The most frequently affected cognitive areas are attention, executive functions, speed of data processing, working and episodic memory tasks and visuospatial capabilities, with language and general intelligence being relatively spared [2,3].
Genetic factors are one of the various risk factors affecting cognition in MS patients. The brain-derived neurotrophic factor (BDNF) is a neurotrophin protein primarily secreted in the brain by several cell types. It plays an important role in the growth and survival of neurons and oligodendroglia in normal brains as well as other neurologic diseases [4].

The BDNF single-nucleotide polymorphism rs6265 (also called Val66Met) is a G-to-A replacement leads to production of amino acid methionine instead of valine at the 66thcodon of the BDNF pro-protein [5]. This interferes with intracellular trafficking and leads to 18–30% reduction in the secretion of BDNF as it has been demonstrated in many studies [5,6].

It has been noted that Val66Met polymorphism is a risk factor for various neurodegenerative disorders including early onset Alzheimer's disease [7]. Moreover, it has been associated with cognitive deficits of the episodic and working memory in brain areas of healthy population where excess production of BDNF is needed for neuroplasticity [8,9].

BDNF has a fundamental role in some neuro-inflammatory and autoimmune disorders, especially MS. Some studies support its correlation with cognitive performance and brain atrophy measures, with ambiguous results [9-11].

Our current study was designed to assess the role of the previously mentioned polymorphism on deterioration of cognition and disability in MS patients.

METHODS

This case control study involved 100 participants (50 MS patients and 50 Healthy controls). MS patients were recruited from MS units of Kafrelsheikh and Zagazig University Hospitals. Approval from the local Ethical Committees (ZU-IRB#9608) and written informed consents from the participants were obtained.

Inclusion criteria: Age >18 years with no history of intellectual dysfunction, psychosis, dementia and not taking methyl prednisolone pulse therapy. MS diagnosis was based on McDonald 2017 [12].The patients' clinical and demographic data were recorded, including age, gender, type of MS, number of relapses in the last two years, total number of relapses, disease duration. Patients were carefully evaluated and given a score of EDSS during their first visit.

The control group involved 50 healthy individuals free of any neurological or psychiatric illness. They were of the same age group, same level of education and came to the hospital for regular health checkup during the same time of the study.

Clinical and Cognitive Assessment:

The degree of disability of our patients was assessed using the Expanded Disability Status Scale (EDSS) scale [13]. The scale evaluates eight functional systems to measure impairment with lower scores indicating lower grades of disability and higher score indicating progressive disability up to death. An EDSS score of 6.0 is important as it is a marker for the need for walking aids [14]. The Multiple Sclerosis Severity Score (MSSS) was calculated by adding EDSS score to the disease duration [15].

The "Brief International Cognitive Assessment for MS" (BICAMS) was assessed for all study participants. The test is widely used to detect cognitive impairment (CI) in MS patients [16,17]. It is composed of three subtests covering specific cognitive domains: Complex attention and information processing speed by the Symbol Digit Modality Test (SDMT) [18], verbal learning and memory by the California Verbal Learning Test (CVLT-II) [19], and visuo-spatial memory using the Brief Visuospatial Retention Test revised (BVRT-R) [20]. The three subscales were performed in the same previously mentioned order following its validated Arabic version [21].

Radiological investigations included MRI of brain and spinal cord. A standardized protocol of 1.5 Tesla MRI scanning comprising T2-weighted and T1-weighted gadolinium enhancing with axial, sagittal and coronal sections, fluid accentuated inversion recovery images (sagittal flair) were performed.

Genetic analysis:

Five ml of EDTA blood was collected from each patient and stored at -80 ^{O}C. DNA was isolated using gSYNC™ DNA Extraction kit (Geneaid, New Taipei City, Taiwan) according to the manufacturer's instructions.

BDNF polymorphism

Genotyping of BDNF Val66Met was performed via polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). PCR reaction was executed using the gene-specific forward primer (FP)-5′ACTCTGGAGAGCGTGAATGG3′ and reverse primer (RP)-5′ACTACTGAGCATCACCCTGGA3′ [22]. The mixture for PCR was prepared in a total volume of 20µl including: 5µl of template DNA, 10 µl of PCR master mix and 1 µl of each primer, completed with nuclease free water up to 20µl. The thermal cycling conditions were an initial denaturation step at 95°C for 5 minutes, 35 cycles of DNA denaturation at 95°C for 30 seconds, annealing at 60°C for 30 seconds, extension at 72°C for 1 min, then finally 10 minutes of final extension at 72°C.PCR products (171 bp) underwent gel electrophoresis and visualization under UV light.

The PCR products were then digested with restriction enzymeEco72I as per the manufacturer's

protocol (Eco72I; Thermo Scientific, USA). The digestion products were analyzed by electrophoresis on 2% agarose gel. The uncut allele 'A'(Met) was 171 base-pairs (bp) long, while the allele 'G' (Val) comprised cut bands of 99 bp and 72 bp.

In our study, 3 genotypes were identified. First was the homozygous Val66Val genotype. Second was the heterozygous Val66Met and the last was the homozygous Met66Met genotype. And as shown in previous studies that the presence of the Met allele produced reduction of BDNF secretion [6] and for the purpose of easy categorization, we divided patients into two groups: The Val66Val group and the met carrier group.

Statistical analysis:

Categorical variables were summarized as frequencies (Percentages). Quantitative variables were represented as mean (SD) or median (IQR) according to results obtained from normality test. Relationships between variables were obtained using t-test, Mann Whitney U test for continuous variables and Chi-square or Fisher's exact test for categorical variables. Predictors of disability were estimated using regression analysis test.

RESULTS

Table 1 compared the genotype distribution and BICAMS test results between 50 MS patients (36 females and 14 males) and 50 control healthy volunteers. It showed that MS patients had significantly low score on the SDMT, CVLT, and BVRT-R tests, P values were 0.0001, 0.02, and 0.0001, respectively. Val/Val genotype frequency represented the majority among cases and healthy control (70% and 84% respectively). Figure (1) showed the BDNF genotyping by restriction fragment length polymorphism. Table 2 described the clinical features of MS patients. The age of onset of disease was 27.9±8.6, RRMS represented 35 (70.0%) of our patients with median disease duration of 4 years. 58 % of our patients had active lesions on MRI and 50% had a high lesion load. The EDSS in our patients ranged from 0.5 to 6.5.

Table 3 showed that age, gender, MS subtype, age of disease onset, disease activity in MRI and the presence of high lesion load did not differ between the two groups. Val/Val genotype had significantly higher number of relapses (P=0.017) and met allele group of patient had significant longer disease duration (P=0.009). Although, the met carrier patients' group had higher disability measured by EDSS and MSSS and higher cognitive dysfunction measured by BICAMS, only significant associations could be detected on the SDMT of BICAMS (P=0.04).

We used logistic regression analysis to estimate factors predicting disease disability. We found significant association with higher number of relapses, disease activity on MRI brain represented by high lesion load and the presence of cervical lesion. On the other hand, neither Val/Val genotype nor met allele carrier patients could predict clinical disability (P=.157, 0.099 respectively) Table (4).

Table (1): The clinical characteristics, genotype distribution and cognitive assessment of patients and controls.

Variables	Cases (N= 50)	Controls (N=50)	P- value
Age, years, mean ±SD	33±9.6	29.8±7.1	0.063
Females, n (%)	36 (72)	30 (60)	0.21
BDNF genotype frequency			
Val/Val genotype, n (%)	35(70.0)	42(84.0)	P=0.095
Met carrier, n (%)	15(30.0)	8(16.0)	
BICAMS			
SDMT, mean ± SD	20.8±11.4	36.8±9.9	0.0001*
CVLT mean ± SD	43.9±15.8	49.3±11.3	0.02*
BVST-R, mean ± SD	20.5±8.6	27.8±6.5	0.0001*

BDNF: Brain derived neurotrophic factor
SDM: Symbol digit modality test
CVLT: California verbal learning test
BVST-R: Brief visuospatial test revised

Table (2): Distribution of clinical, radiological features, disease severity and disability among our MS patients.

Variables	Cases (N= 50)
Type of MS	
CIS, n (%)	2(4.0)
RRMS, n (%)	35(70.0)
PPMS, n (%)	2(4.0)
SPMS, n (%)	11(22.0)
Age at onset, years, mean ±SD	27.9±8.6
Disease duration years, median (IQR)	4(0-24)
No of relapses in the past 2 years, median (IQR)	2(0-5)
Total No of relapses, mean±SD	3.9±.9
MRI activity, n (%)	29 (58)
Presence of high lesion load, n (%)	25(50)
Site of the Lesions	
Periventricular	47(94)
Juxtacortical	42(84)
Infratentorial	18(36)
Cervical	16(32)
EDSS score, median (IQR)	2(.5-6.5)
MSSS, mean±SD	4.3±2.6

CIS: Clinically isolated syndrome
RRMS: Relapsing remitting multiple sclerosis
PPMS: Primary progressive multiple sclerosis
SPMS: Secondary progressive multiple sclerosis
EDSS: Expanded disability status scale
MSS: Multiple sclerosis severity scale

Table (3): Distribution of the Clinical characteristics, disease disability, and cognitive functions of MS patients according to BDNF Val66Met polymorphism.

Variables	Val/Val genotype (N=35)	Met allele carrier (N=15)	P-value
Age, years, mean ±SD	32.1±9.9	35.3±8.7	0.29
Females, n (%)[a]	26(74.3)	10(66.7)	0.73
Type of MS			
CIS, n (%)	2(5.7)	0 (0.0)	0.16
RRMS, n (%)	26(74.3)	9(60.0)	
PPMS, n (%)	2(5.7)	0 (0.0)	
SPMS, n (%)	5(14.3)	6(40.0)	
Age at onset, mean ±SD	28.1±9.4	27.5±6.4	0.89
Disease duration years, median (IQR)	3(0-15)	7(1-24)	**0.009***
No of relapses in the past 2 year, median (IQR)	2(0-5)	2(0-4)	0.38
Total No of relapses (mean)	3.5±1.9 4(1-8)	2±1.1 2(0-4)	**0.017***
MRI activity, n (%)	20(57.1)	9(60.0)	0.85

Presence of high lesion load, n (%)	17(48.6)	8(53.3)	0.76
EDSS score, median (IQR)	2(0.5-6)	3.5 (1-6.5)	0.104
MSSS, mean ±SD	4.2±2.7	4.5±2.4	0.458
SDMT, mean ±SD	22.6±11.4	16.7±10.6	**0.04***
CVLT, mean ±SD	46.5±15	38±16.2	0.055
BVST-R, mean ±SD	21.6±8.2	18.1±9.3	0.109

EDSS: Expanded Disability Status Scale.
MSSS: Multiple sclerosis severity scale
BDNF: Brain derived neurotrophic factor
SDMT: Symbol digit modality test
CVLT: California verbal learning test
BVST-R: Brief visuospatial test revised
*P<0.05 is meant significant

Table (4): Logistic regression analysis for prediction of disease disability by EDSS.

Variables	P	Exp(B)	95% C.I.for EXP(B)	
			Lower	Upper
Age of onset	.193	1.050	.975	1.13
Disease duration	.078	1.171	.983	1.39
Total No of relapses	**.011***	1.705	1.132	2.57
MRI activity	.157	2.597	.692	9.75
Presence of high lesion load	**.037***	4.125	1.092	15.58
BDNF Met allele polymorphism	0.099	2.953	.82	10.68
BDNF Val/Val polymorphism	.157	2.597	.692	9.75
Cervical lesion	**.001***	9.667	2.414	38.71

EDSS: Expanded Disability Status Scale
BDNF: Brain derived neurotrophic factor
Exp(β)=the odds ratios for the predictors
CI=Confidence interval
*p<0.05 significant predictors

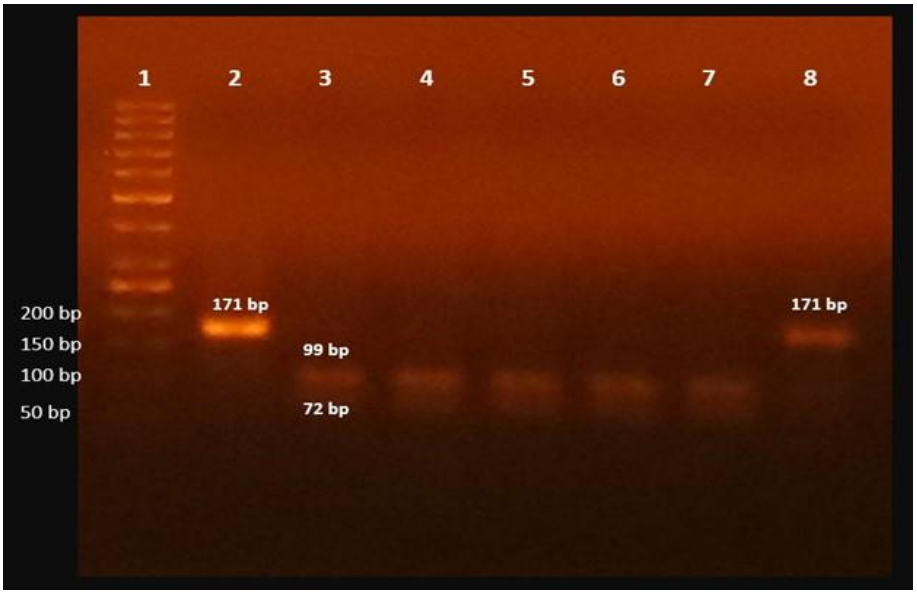

Figure (1): BDNF genotyping by restriction fragment length polymorphism. Lanes 1 is DNA Ladder. The wild BDNF allele (G) is cut into two fragments with Eco 72 I, 99 bp and 72 bp, seen in lanes (3-7). The mutant allelic variant (A) remains uncut, seen in lanes (2 &8).

DISCUSSION

The BDNF Val66Met polymorphism is closely linked to neurodegenerative diseases such as multiple sclerosis, Parkinson's disease and Alzheimer's disease [23-25]. The methionine-containing variant (Met Carrier) replaces the amino acid valine for methionine which results in defective activity dependent secretion of secretory granules at synapses [5].

The goal of the study was to determine if polymorphism of the BDNF rs6265 in MS patients reflect the disability and cognitive decline, using approved clinical and neuropsychological tests.

In our study, The BDNF Met carrier group of patients were associated with a significant lower score on SDMT. Also, BDNF Met genotypes displayed smaller scores in CVLT and BVST-R tests in comparison to Val/Val homozygotes, but the effect was insignificant.

Similar research revealed a direct correlation between low levels of BDNF and low performance on memory and executive tests [26, 27]. It is not yet apparent whether having the Met allele is harmful to all cognition domains or not [28, 29]. A large Norwegian study revealed that the above-mentioned polymorphism did not have any effect on cognitive and clinical characteristics [30].

Upon studying structural MRI in healthy persons, they found that Met carriers' patients had decreased volume of the dorsolateral prefrontal cortex (DLPFC) and the hippocampus, the structures responsible for learning and working memory [31, 32]. In addition, several functional magnetic resonance imaging (fMRI) studies revealed the same alteration of neurophysiological activity in the same areas [5, 8].

On the other hand, results from different investigations point to the BDNF Val/Met polymorphism as a protective factor against MS patients' cognitive loss and brain atrophy [33, 35]. Another study exploring Met carriers showed that they had higher gray matter volumes [10]. They provided evidence to support their findings by pointing out that BDNF in MS patients may differ dramatically from that in healthy people and people with other diseases. Higher BDNF mRNA expression by the neuro-inflammatory cells in MS leads to higher BDNF release [36]. However, depending on its concentration and the expression of two distinct BDNF receptors, the p75 neurotrophin receptor (NTR) and the TrKB receptor [37,38], the BDNF may play two different roles in the context of neuro-inflammation. The two receptors mediate two distinct actions and have varying affinity for BDNF. Specifically, the pro-apoptotic activity of the p75 NTR is believed to be mediated by interacting with BDNF at greater concentrations, whereas the activity of TrKB receptor is apparent at low BDNF concentrations. This regulates the rows of signals linked to survival of neurons [35].

Furthermore, BDNF increases transmission of glutamate at the synapse [39] and glutamate excitotoxicity can cause oligodendrocytes and neuronal loss in MS patients, [40]. Therefore, elevated BDNF synthesis in the setting of neuro-inflammation may be harmful, pushing toward cell death and apoptosis. These behaviors may impair cognitive abilities and lead to neuropsychological impairment [35].

Liguori and colleagues showed in a group of 50 RRMS patients that the Met66 allele was linked to a lower GM volume. However, neither RRMS patients nor controls showed any BDNF-related effects on global cognitive functions [22]. The differences between our results and their study are that we did not perform volumetric study of the brain in our MS patients. We included in our study all types of multiple sclerosis with different grades of disability. Liguori and colleagues included only RRMS with minimal clinical disability. Also, the battery of neuropsychological tests used was different.

MRI is a required diagnostic tool for MS patients to evaluate the course and activity of the disease [41]. The T2 lesions load is thought to be the strongest indicator of MS activity, and to have a strong link with disease disability in long term follow up [42]. Our study showed no difference between BDNF genetic variants and both the presence of activity in neuroimaging and the T2 lesion load. In accordance with our results, Naegelin and his colleagues could not find a relation between BDNF levels and the T2 lesion volume and new/enlarging T2 lesions [43]. On the other hand, Sarchielli *et al*. reported a significant association between the levels of BDNF and the presence of gadolinium enhancing lesions on MRI [44].

The variation in results could be explained by several factors. The different sample size of each study. Also, manual counting of MRI lesions could differ between physicians and is not an accurate method to rely on. Furthermore, the impact of disease modifying therapies (DMT) on BDNF levels was not evaluated. Among the currently used DMT is the glatiramer acetate (GA), which might promote BDNF production by activation of Th1 and Th2 lymphocytes [45]. Current hypotheses suggest that Th2 cells stimulated by GA enter the central nervous system and, through a process known as "bystander suppression," release anti-inflammatory cytokines that inhibit nearby inflammatory cells [46].

In our work, the presence of rs6265 SNP did not predict a more severe disability score. Nicoti and colleagues showed that this polymorphism when taken by itself does not link to a more severe EDSS score but the methylation level of the BDNF gene is the link to the disability [47].

Our study had some limitations. The first being the small sample size. Secondly, we did not measure the serum level of BDNF in our patients to assess variations in levels among different genotypes. Third, although we assessed MS patients not on steroid pulse therapy, to avoid confounding results, we did not evaluate the role of different types of DMT. Further studies focusing on large groups of multiple sclerosis patients on both remission and relapses with consideration of the type and duration of DMT should be considered.

CONCLUSIONS

Our study could not demonstrate a significant relationship between rS6265 polymorphism and MS disability. The defects in complex attention and the information processing speed domains of cognition were related to the met carrier patients.

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