Significant Destructive Interaction of BDNF Val>Met Polymorphism with Stroke Severity and Family History of Dementia for Cognitive Impairments

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Abstract

Purpose: The patients with more severe stroke, have more chance to develop higher levels of cognitive impairments; and family history of dementia as a genetic background, can give rise to an increased risk of the severity of cognitive deterioration. In this study, we sought to investigate whether the risk alleles of Val66Met of brain-derived neurotrophic factor(BDNF) polymorphism, has a destructive interaction with the stroke severity(SS) and family history of dementia(FHD) for cognitive impairments?

Method: In a case-control study, the carriers of at least one Val allele(n=56) were compared to the carriers of Met/Met homozygotes(n=156) in terms of FHD and SS(through National Institutes of Health Stroke Scale) on the north of Iran. To determine the cognitive functions, the third version of Addenbrooke's Cognitive Examination(ACE-III) was used..

Result: The mean age of patients was 64.52±11.71,and in average 202 day had passed from their stroke. The interactive effects of genotypes Val66Met BDNF with SS[$F=8.95$,$\acute{\eta}^2=0.04$, $P=0.003$] and FHD[$F=4.59$,$\acute{\eta}^2=0.02$, $P=0.03$] were significant for total score of ACE-III. It means that the Met/Met homozygosity, modulated the effect of risk factors of SS and FHD on the cognitive function. Such homozygosity protects the attentional function and language abilities against the SS and FHD($P\leq0.05$).

Conclusion: It can be speculated that presence of Val/Met heterozygosity has a destructive interaction with the SS and FHD for decreasing the cognitive function, particularly in attention and language domains. Our findings suggested that the inhibition of signaling and trafficking of Val/Met heterozygosity is possibly a practical strategy in reducing the cognitive impairments following the stroke.

Keywords: Stroke; Brain-Derived Neurotrophic Factor; Cognitive Impairment; Polymorphism.

Acta Neurol Taiwan 2020;29:67-78

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Received April 1, 2020. Revised May 18, 2020.
Accepted August 25, 2020.

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INTRODUCTION

The stroke severity can range from mild to severe and fatal. It is now recognized that severe forms of stroke, can lead to profound cognitive impairments, and it is acknowledged as a crucial factor in vascular dementia [1,2,3]. Further studies demonstrated that the severity of neurological impairments measured in acute phase of stroke, was more advantageous in anticipating the subsequent cognitive impairments in the next 3 to 6 months, in comparison to the time of discharge [4,5]. Furthermore, Dong et al., [6] by inspecting milder forms of stroke patients found that the patients' scores in cognitive tests implemented on the patient admission were better predictors for their cognitive impairments in the next 3 to 6 months than the discharge time. In a meta-analysis by Pendlebury & Rathwell [7], the severity of stroke was determined as a significant prognosticator of post-stroke dementia.

Evidence has shown that the cognitive changes in the old age and post-stroke cognitive impairments can be exacerbated as a consequence of family history of dementia and Alzheimer [2,8,9]. Recent researches suggested that the stroke patients with family history of dementia may experience the dementia even before occurrence of their stroke; hence, the family history of dementia seems to be an intensifying factor at the start of vascular pathological processes and neural degeneration [7,10]. Okonkwo et al., [11] showed that family history of Alzheimer is able to predict the hippocampus atrophy among the middle-aged adults who are not suffering from stroke.

Researchers believe that the serious post-stroke consequences can be modulated by the neurotrophic factors [12,13,14], for the reason that its neuroplastic effects play a critical role in improvement of vascular accidents [15]. The brain-derived neurotrophic factor (BDNF) is the most frequent neurotrophic factor inside the brain, and since animal studies found that BDNF had a facilitating role in the angiogenesis and neurogenesis, accordingly it is necessary for the improvement of post-stroke cognitive dysfunctions [16,17].

In the previous studies, it is recognized that polymorphism in BDNF gene results in both the increased risk of post-stroke cognitive disorders [14], and impairment in a spectrum of cognitive functions [12]. Most studies have focused on the impacts of a special polymorphism on BDNF gene, in which a variation in the protein structure changes the protein through substituting the Valine amino acid with Methionine amino acid in codon 66 which is written as Val66Met. Such variation damages the protein ability for proper functioning [18,19].

For several reason, BDNF is seen as a very appropriate candidate for examining the post-stroke events. Firstly, it was found out that BDNF protein has a protective role against the brain damages following the ischemic stroke [20,21], and reduces the risk of apoptosis in cultured neurons after the glucose reduction [22]. Additionally, the BDNF signaling pathway is highly connected to neurogenesis in hippocampus [23]. The brain-derived neurotrophic factor (BDNF) gene improves the performance of damaged cortical neurons after the stroke through regulating the BDNF protein expression as well as adding phosphorylation of its receptor [24].

Although it becomes clear that post-stroke cognitive impairments are highly prevalent [14,25] and polymorphism in BDNF gene have a worsening effect on cognitive impairments [12,26], but we think that there is limited information in these literature for the interaction of different variants of this gene with the severity of stroke and family history of dementia. Accordingly, in this study we tried to find an answer for the possible destructive interactions of BDNF variants with the stroke severity and family history of dementia in a range of cognitive impairments.

MATERIALS AND METHODS

participants

The present study is a subproject of previously-published research [12]. The population included all of the patients who have been discharged from the Neurological Department Clinic of Poursina Medical and Educational Center in Rasht, north of Iran. They were diagnosed with the ischemic stroke two years before the study (N = 2920). This was a hospital based case-control study, in which 206 patients with consecutive stroke were selected from all patients through the telephone contact. The research proposal was confirmed by the Ethical Committee of Guilan University of Medical Sciences with regards to

the Helsinki Declaration [No. 1930162907]. The Poursina hospital is the biggest medical and educational center for neurology and trauma in the Northern Iran which provides easy accessibility for people from any socio-economic class (http://www.gums.ac.ir/poursina).

The inclusion criteria were: (1) ischemic stroke confirmed by the neurologist using the CT Scan and/or MRI in accordance with the diagnostic criteria of American Stroke Association (27); (2) having at least the elementary school degree for completing the evaluations and tests needed for this study; and (3) informed consent. The exclusion criteria were: (1) severe loss of consciousness; (2) severe hearing or visual damage, which would make the patient unable to go through tests and evaluations; (3) dementia or other neurological disease before the stroke (like epilepsy, Parkinson's Disease); (4) severe psychiatric disorders which can lead to disturbance of cognitive judgment (like major depression or schizophrenia); (5) continuous and severe aphasia or getting the score ^{3} 3 in language item of National Institutes of Health Stroke Scale (NIHSS).

Procedure

Once the telephone contact was made and patients or their healthcare providers were interviewed, the dead patients or those who had language deficits and severe physical disability, intense dementia/Alzheimer were screened and finally, 206 patients expressed their consent to participate in the study and their blood sample were collected. There was no significant difference among the participants and those who were screened in terms of age and gender ($P > 0.05$). All patients were asked to attend the neurological examination together with one of their family members who had lived with them for at least 10 years.

Neurological and cognitive evaluations

The stroke severity was measured using National Institutes of Health Stroke Scale (NIHSS) by a neurologist [(28)]. The scores ranged between 0 and 42, where the higher scores indicated the more neurological problems. The information concerning the severity of stroke severity was not available for all patients at the time of admission, for this reason we used the recorded information from patient's files at the time of discharge. In this study, the proposed cutoff points were 0-4, 5-15 and 16 and higher, which were used for mild, moderate and severe forms of stroke, respectively. It was due to the fact that neurological prognosis usually is predicted according to three states of desired, moderate and undesired [(29,30)]. Persian version of NIHSS was reported as a reliable and valid instrument, for both male and female patients with stroke [(31)].

Once all neurological examinations for patients were made, they were guided to a trained psychologist. Family history of dementia was determined by a structured interview and examination of medical records and affected family members according to the practical guidance of DSM-5.

To investigate the participants' cognitive performance, the results of third version of Addenbrooke's Cognitive Examination (ACE-III) were applied, because it was found that ACE-III gives a more profound and more accurate neuropsychological measurements in five functions of attention, memory, verbal fluency, language and visuospatial in comparison to MMSE [(10)]. Items of this test were modified for Persian speakers [(32)]. Lower scores in ACE-III indicated worse cognitive functions.

Genotyping

In order to determine the genotype of single-nucleotide polymorphism Val66Met for BDNF gene, PCR-FRLP technique was used. PCR Setup was made with Master Mix kit, Fermentas Co., and designing one pair of synthetized primer F:CATTGGAACTCCCATTGCCGA' and R:AGGACGCAGACTTGTACACG' was manufactured by TAG Co. (Copenhagen, Denmark).

Statistical Analyses

In order to evaluate genotype and allele frequency of the variant of Val66Met, and examination of genotypic distribution for Hardy-Weinberg equilibrium, SNPAlyze software was used (Dynacom, Yokohama, Japan). To answer the main question of study, firstly one-way analysis of variance (ANOVA) was conducted for the total score of ACE-III test to prevent the multi-collinearity error and then, multivariate analysis of variance (MANOVA) was carried out for its subscales. The identification of univariate and multivariate outliers was conducted by Box Plot and Mahalanobis distance calculation, respectively. All of the statistical assumption were examined, but in this

study, only the main output of multivariate analyses was presented and interpreted. To explore the interactive effects of Val66Met polymorphism for BDNF gene with stroke severity and family history of dementia, the 2×2 factorial designs were used separately on each of dependent variables. Effect size for each of genotypic factor, phenotypic factor and their interactions were calculated by Partial Eta Squared ($\acute{\eta}_p^2$) and values higher than 0.010, 0.060, 0.138 were interpreted as the small, medium and big effect size, respectively [33]. These statistical analyses were made with significance level of 0.05 using the SPSS (Ver.20).

RESULTS

The patients included 99 females and 107 males with the mean age of 64.52 ± 11.71 whose ages ranged from 37 to 89 years old. 99 patients (48.1%) were females and the remaining were males. Forty-six patients (22.3%) were divorced or separated and the remaining lived with their spouses or families. The average score of NHISS was 2.50 ± 2.52, fluctuating between 0 to 11. In accordance with the cutoff point mentioned in the "Method" section, 172 patients had mild stroke (0-4), 34 had moderate stroke (5-15) and no one had experienced the severe stroke based on the NIHSS scores. The interview results based on the DSM-5 criteria revealed that 24 patients (12%) has family history of dementia and the others had no such background. BDNF genotyping results clarified that 156 and 50 patients carried the Met/Met homozygote and Val/Met heterozygote, respectively, and no one carried the Val/Val homozygote. The χ^2 goodness of fit test showed that the distribution of various genotypes of Val66Met polymorphism for BDNF gene for the patients is out of Hardy–Weinberg equilibrium (χ^2= 3.93, df=2, P=0.047). Table 1 compares the frequencies of BDNF genotypes in terms of stroke severity and family history of dementia through χ^2 test with Yates correction.

In accordance with table 1, there was no significant differences in the frequency of the variant of Val66Met BDNF genotypes in terms of stroke severity and family history of dementia (P > 0.05). Table 2 shows the mean and standard deviation (SD) of total score of ACE-III and its subscales in two groups of Val/Met heterozygotes (n = 50) and Met/Met homozygotes (n = 156) based on the various levels of stroke severity and family history of dementia.

According to table 3, ANOVA results within a 2×2 factorial design showed that the main effect of stroke severity on total ACE-III score is significant [F = 12.64, $\acute{\eta}^2$ = 0.06, P < 0.0001] and if we look back on the means of table 2, it can be acknowledged that the patients with moderate stroke have more cognitive impairment than those with mild stroke (25.58 vs. 45.69). Based on the Eta squared, it can be said that 6% of difference was resulted from the impact of stroke severity. However, the main effect of family history of dementia on the total ACE-III was not significant [F = 2.98, $\acute{\eta}^2$ = 0.02, P < 0.086]. The main effect of Val66Met BDNF genotypes on total ACE-III score was significant in group comparisons based on the stroke severity and family history of dementia (P < 0.001). In the other words, it means that the carriers with at least one Val allele have weaker general cognitive function compared to the Met/Met homozygotes (38.90 Vs. 48.22). Based on the Eta squared, it can be said that 5% to 8% of difference was resulted from the impact of the polymorphism. However, the calculated F ratio for interactive effects of Val66Met BDNF genotypes with stroke severity [F = 8.95, $\acute{\eta}^2$ = 0.04, P = 0.003] and family history of dementia [F = 4.59, $\acute{\eta}^2$ = 0.02, P < 0.03] for total ACE-III score was significant; implying that the homozygous Met/Met presence modulates the effects of risk factors of stroke severity and family history of dementia on the cognitive function.

To investigate the significance of main and interactive effects of Val66Met genotypes with stroke severity and

Table 1. Comparing the frequencies of BDNF genotypes in terms of stroke severity and family history of dementia

Characteristics	Met/Met (n=156)	Val/Met (n=50)	P-value
Stroke severity, Mild/Moderate	128/28	44/6	0.443
Family history of dementia, Yes/No	58/98	14/36	0.310

Table 2. Mean and standard deviation (SD) of total score of ACE-III and its five subscales for Val66Met polymorphism genotypes, various levels of stroke severity and family history of dementia

variables	categories	Val66Met Genotypes	Attention M±SD	Memory M±SD	Fluency M±SD	Language M±SD	Visuospatial M±SD	ACE-III total score M±SD
Stroke severity	Mild (n=172)	Val/Met	10.84±4.37	9.39±6.65	2.93±2.56	14.00±6.68	5.52±3.81	42.68±20.97
		Met/Met	12.25±3.40	12.43±7.30	3.31±2.40	14.95±6.11	5.76±4.14	48.71±20.11
	Moderate (n=34)	Val/Met	2.83±3.43	2.17±3.71	0.50±0.83	4.33±4.80	1.33±2.06	11.17±13.29
		Met/Met	10.50±4.31	11.86±6.31	2.96±2.80	15.64±6.01	5.03±3.40	46.00±18.46
Family history of dementia	No (n=181)	Val/Met	10.70±4.59	12.37±7.49	2.85±2.37	13.73±7.07	5.39±3.85	42.29±20.98
		Met/Met	12.31±3.73	12.32±7.10	3.24±2.34	16.00±6.25	6.00±4.07	50.00 ±21.11
	Yes (n=24)	Val/Met	6.12±5.59	9.60±6.22	1.87±3.35	8.62±7.00	3.50±3.96	23.87±26.15
		Met/Met	11.89±3.62	13.75±7.75	3.31±2.47	14.97±6.07	5.59±4.02	48.02±19.71

Table 3. two-way ANOVA results for determining the main and interactive effects of Val66Met polymorphism genotypes of BDNF gene with various levels of stroke severity and family history of dementia on the total ACE-III score

Sources	df	MS	F	$\acute{\eta}^2$	P-value
Stroke severity	1	5029.29	12.64	0.06	0.0001
Val66Met Genotypes	1	6871.71	18.02	0.08	0.0001
Stroke severity × Val66Met Genotypes	1	3562.08	8.95	0.04	0.003
Family history of dementia	1	1233.81	2.98	0.02	0.086
Val66Met Genotypes	1	4632.46	11.21	0.05	0.001
Family history × Val66Met Genotypes	1	1899.29	4.59	0.02	0.03

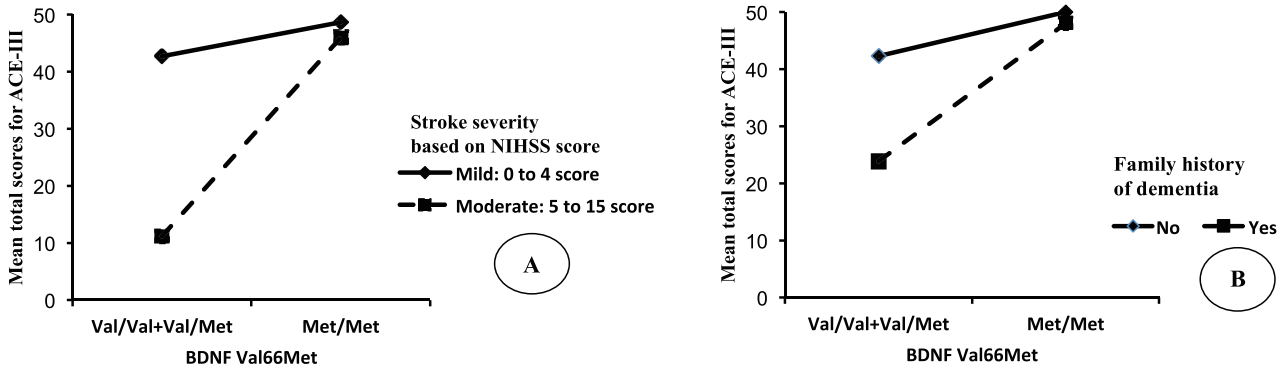

Figure 1. Interactive impacts of Val66Met BDNF genotypes with stroke severity (A) and family history of dementia (B) on total ACE-III score

family history of dementia on the total ACE-III score, the interactive effect diagram was used, which its results are given in figure 1. It should be added that the results of Levene's test demonstrated that the error variances of groups with mild to moderate stroke (F = 0.634, df1 = 3, df2 = 202, P = 0.594) and groups with and without the family history of dementia (F = 0.272, df1 = 3, df2 = 201, P = 0.845) are equal for total ACE-III score.

With regards to figure A1 and information given in table 2, the interactive effects of stroke severity and various Val66Met genotypes shown that the mean total ACE-III score in carriers with at least one Val allele and at the same time higher stroke severity, was significantly lower than the Met/Met homozygotes. Furthermore, figure B1 and information given in table 2 for the interactive effect of family history of dementia and various Val66Met genotypes shown that the average total score of ACE-III test among the carriers with at least one Val allele and family history of dementia was significantly lower than the Met/Met homozygotes.

Before implementing the MANOVA, it became clear that Box's M statistic was not significant (P < 0.0001, Box's M = 152.929, F = 3.197) indicating the covariance matrices of dependent variables in various levels of stroke severity (Box's M = 40.35, F = 1.27, P = 0.149) and family history of dementia (Box's M = 54.57, F = 1.02, P = 0.437) were equal. The Levene's test also clarified that the error variances of groups were equal for all dependent variables (P > 0.05); hence the Wilk's lambda (λ) test was used to determine the significance of multivariate effects. The range of correlations observed among the dependent variables was 0.54 to 0.72. The result of Bartlett's test of sphericity suggested that there were enough correlations among the dependent variables in stroke severity (χ^2=867.18, df=14, P<0.0001) and family history of dementia (χ^2=863.92, df=14, P<0.0001).

Table 4. Two-way MANOVA results for determining the main and interactive effects of Val66Met polymorphism genotypes with different levels of stroke severity and family history of dementia on the ACE-III subscales

Sources	Dependent variables	df	MS	F	$\acute{\eta}^2$	P-value
Stroke severity	Attention		408.77	28.95	0.12	0.0001
	Memory		260.68	5.37	0.03	0.022
	Verbal Fluency	1	33.18	5.90	0.03	0.016
	Language		345.98	9.02	0.04	0.003
	Visuospatial Abilities		103.90	6.70	0.03	0.010
Val66Met Genotypes	Attention		353.63	25.05	0.11	0.0001
	Memory		696.16	14.34	0.07	0.0001
	Verbal Fluency	1	34.75	6.17	0.03	0.014
	Language		645.59	16.82	0.08	0.0001
	Visuospatial Abilities		66.83	4.31	0.02	0.039
Stroke severity ×	Attention		168.11	11.91	0.06	0.001
Val66Met Genotypes	Memory		189.70	3.91	0.02	0.049
	Verbal Fluency	1	18.64	3.31	0.02	0.070
	Language		460.48	12.00	0.06	0.001
	Visuospatial Abilities		51.38	3.32	0.02	0.070
Family history of	Attention		79.11	5.13	0.02	0.025
dementia	Memory		153.91	3.15	0.01	0.077
	Verbal Fluency	1	3.77	0.65	0.01	0.419
	Language		75.93	1.89	0.01	0.170
	Visuospatial Abilities		10.04	0.63	0.01	0.428
Val66Met Genotypes	Attention		0.248	7.40	0.07	0.0001
	Memory		586.76	3.26	0.06	0.001
	Verbal Fluency	1	15.23	0.87	0.01	0.105
	Language		338.82	4.28	0.04	0.004
	Visuospatial Abilities		33.35	2.09	0.01	0.149
Family history ×	Attention		114.23	7.40	0.04	0.007
Val66Met Genotypes	Memory		159.64	3.26	0.02	0.072
	Verbal Fluency	1	5.01	0.87	0.01	0.352
	Language		171.85	4.28	0.02	0.040
	Visuospatial Abilities		24.09	1.51	0.01	0.220

Hence, the MANOVA was continued. The results of λ test showed that multivariate main effects for stroke severity (λ=0.865, F5,198=6.19, $\acute{\eta}^2$=0.13, P<0.0001) and Val66Met genotypes (λ=0.900, $F_{5,197}$=6.19, $\acute{\eta}^2$=0.12, P<0.001) as well as the interaction of stroke severity × Val66Met genotypes (λ=0.929, $F_{5,198}$=6.19, $\acute{\eta}^2$=0.07, P<0.01) were present on the linear combination of dependent variables responsible for 13%, 12% and 7% of total variance. However, such difference was not obtained for the main effect of family history of dementia and interactive effect of family history of dementia ×Val66Met genotypes (P > 0.05).

Table 4 shows the MANOVA results for the main and interactive effects of Val66Met polymorphism genotypes with stroke severity and family history of dementia on various dimensions of cognitive function within a 2 × 2 factorial design. Since we had 5 dependent variables, the Bonferroni alpha was adjusted on 0.01 to make us able to determine the significance level (adjusted P-value =α/5)

As can be noticed in table 4, the main effect of stroke severity had a significant impact on the scores of attention, verbal fluency, language and visuospatial abilities (P < 0.01). Meanwhile, according to table 2, the moderate stroke group has obtained lower scores in cognitive fields than the mild stroke group. The main effect of Val66Met polymorphism of BDNF gene also influenced significantly the scores of attention, memory and language (P < 0.01). For this reason, it can be concluded that the carries of at least one Val allele have obtained lower scores compared to the Met/Met homozygotes. Furthermore, the F ratio calculated for interactive effects of stroke severity × Val66Met genotypes was significant. Finally, the interactive effects of family history of dementia × Val66Met genotypes on the attention score [F=7.40, ήp2=0.04, P=0.007] were significant. These results indicated that Met/Met homozygote presence modulated the impact of risk factors of stroke severity and family history of dementia on the cognitive functions of attention and language. Nonetheless, it is necessary to be precautious in interpreting these results due to the low values of Eta squared. Figure 2 is a schematic diagram representing the significant main and interactive effects of Val66Met genotypes with stroke severity and family history of dementia on the scores of ACE-III subscales.

Figure 2A and B as well as the information given in table 2, for the interactive effects of stroke severity and various Val66Met genotypes showed that the mean scores of attention and language in the carriers of at least one VA allele with higher stroke severity are considerably lower than the Met/Met homozygotes. In addition, figure 2C and the information given in table 2 for the interactive effects of family history of dementia and various Val66Met genotypes showed that the mean scores of attention among

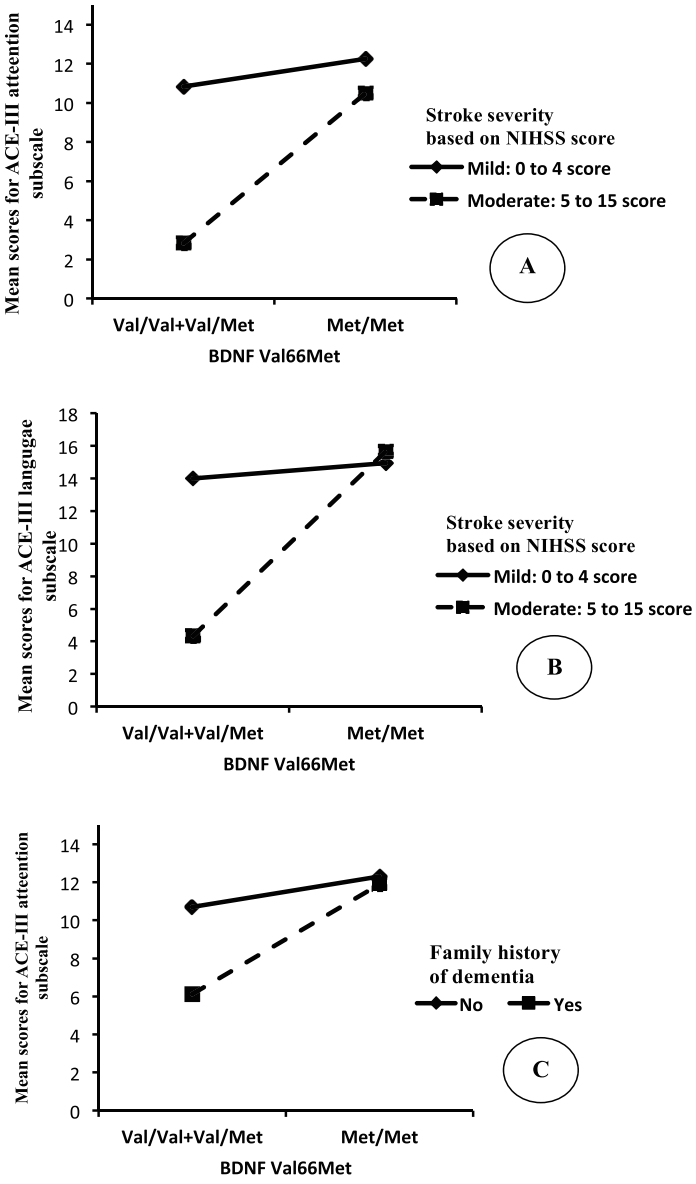

Figure 2. Interactive effects of Val66Met BDNF genotypes with stroke severity on the scores of attention (A) and language (B) as well as the its interactive effects with family history of dementia on the attention (C) scores

the carriers of at least one VA allele with family history of dementia were significantly lower than the Met/Met homozygotes.

DISCUSSION

In previous studies, it became clear that the presence of risk allele of BDNF gene Val66Met polymorphism is able to damage the cognitive functions through making the preparation for degeneration or loss of neuron functioning in brain structures [12,14,34]. It was also found that the risk variant of Val66Met polymorphism was related to the more impairment in episodic memory, encoding ability and information retrieval/recall and executive functions, since that risk variant can lead to shrinkage and decline in hippocampal circuits [35,36]. The present study confirmed the findings of previous researches, but takes step further and emphasized on investigating the destructive integration of BDNF variants with stroke severity and family history of dementia on a range of cognitive impairments.

In this study, the dominant inheritance pattern of BDNF gene Val66Met polymorphism (Met/Met vs Val/Met + Val/Val) was able to modulate the destructive effect of positive family history of dementia on the cognitive impairment, especially the attention function. This research revealed that following the stroke, Met/Met homozygote presence protects the patients with family history of dementia, against the cognitive impairments, especially the in attention function. The destructive role of family history of dementia in cognitive functions has been documented for a long time [8]. Furthermore, some authors reported that the family history of dementia (especially in maternal family) was connected to the biomarkers of Alzheimer disease including sedimentation of Amyloid Beta in middle and posterior areas of temporal lobe, and low metabolism of glucose in the brain [37]. It was also found, that in the cerebrovascular diseases there is usually a family history of dementia, which predicts the risk of hippocampus atrophy [11] and cognitive impairment related to the multiple cerebral infarctions [38]. To the best of our knowledge, no study has been conducted on the modulating effect of BDNF gene Val66Met polymorphism on the family history of dementia and various cognitive functions; but some longitudinal studies on the persons without dementia has revealed that, there is destructive interaction between the family history of dementia and other genetic factors (e,g, e4 variant of APoE gene) that leads to exacerbation of cognitive impairments [39].

One possible interpretation of significant interactive effect between the family history of dementia and Val/Met heterozygosity in this study is that the inherited destructive genetic capacities and common and impoverished intra-familial environment (e.g. low cognitive reserve and low educated family members) can independently lead to the cognitive impairment. These factors, however are not necessarily associated to the stroke, and may be similarly leading to cognitive impairments in some normal situations. Yet, it is not clear which kind of mechanism might be responsible for the relationship between positive family history of dementia and attention dysfunctions. Generally, these findings support the hypothesis that *"the positive family history of dementia among the immediate family members of patients with stroke, can play a critical role in the expression of allele and BDNF risk genotypes related to the cognitive impairment"*. Therefore, paying attention to the positive family history of dementia can be valuable as much as monitoring post-stroke cognitive examinations.

The present study revealed that dominant inheritance pattern for BDNF gene Wal66Met polymorphism is able to modulate the destructive effect of stroke on the cognitive impairment, particularly the functions of attention and language abilities. In other words, findings indicated that following the stroke, Met/Met homozygote protects the patients with more stroke severity from the cognitive impairments, especially the functions of attention and language deficiencies.

It is now acknowledged that the more severe stroke can lead to more profound cognitive impairments due to its serious damages to the consciousness, and sensory-motor, and language parts of the central nervous system [3,40,41,42,43]. Furthermore, the stroke severity is known as a determining factor in vascular dementia [1,7,10,44]. Although the authors have not found a published study regarding the modulating effect of BDNF gene Val66Met polymorphism on the relationship between the stroke severity and various cognitive functions; but it seems that as the stroke severity is exacerbated, the Met/Met homozygosity plays a stable nutritional and protective role for the nervous centers related to the processing of attention and language

production.

Data of this study cannot be generalized to the hemorrhagic stroke patients. The sample size was not large enough to encompass the different BDNF genotypes in dominant and recessive inheritance models, and to compare them in terms of various cognitive functions. There are many confounding factors related to the cognitive function of this study such as age, sex, education, past history of stroke, underlying medical disease including hypertension, diabetes, heart disease etc. Authors could not control the effects of this confounders, because the number of patients was small in each class/ category of BDNF Val66Met polymorphism. Therefore, due to the small sample size, the study lacked sufficient power for us to draw definitive conclusions. The future studies should explore the molecular mechanisms in order to answer this question: how does the BDNF gene Val66Met polymorphism is able to improve the cognitive consequences of stroke through targeting the intracellular signaling and trafficking system of BDNF protein?

CONCLUSION

It is inferred from the findings that among those living on the north of Iran, carriers of at least one Val allele have shown a higher chance of post-stroke cognitive impairments. Val/Met heterozygosity has had a destructive interaction with stroke severity and family history of dementia, and consequently was able to diminish the cognitive function, particularly in the fields of attention and language. From our findings, it can be proposed that inhibition of Val/Met heterozygosity signaling and trafficking might be a possible and practical strategy for improving the post-stroke cognitive impairments. Our results support the idea that BDNF can be effective in improvement of cognitive function through the neurogenesis and regulation of expression level of neurotrophic proteins in ischemic cortex.

Financial disclosure

All authors have nothing to declare for financial disclosure.

Compliance with Ethical Standards

The proposal draft was approved by the ethics committee and research council of Guilan University of Medical Sciences (GUMS) [No. 1930162907].

Conflict of Interest

The authors declare that they have no competing interests.

Acknowledgments

We are deeply grateful to the patients for their participation in this study, the staff of Clinical Research Development Center in PourSina Hospital, and the Social Service Retirees Center in the process of data collection.

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