Brain-Derived Neurotrophic Factor polymorphism methylation in Multiple Sclerosis patients: a marker of disease progression

Nociti V[1,2], Santoro M[2], Quaranta D[1], Losavio FA[1], De Fino C[1], Giordano R[1], Palomba N[1], Rossini PM[1], Guerini FR[2], Clerici M[2,3], Caputo D[2], Mirabella M[1]

- [1]Institute of Neurology, Department of Geriatrics, Neurosciences and Orthopedic, Catholic University, Rome, Italy
- [2]Fondazione Don Gnocchi-ONLUS, Milan, Italy
- [3]Department of Pathophysiology and Transplantation University of Milan, Milan, Italy

OBJECTIVES

Brain-Derived Neurotrophic Factor (BDNF) is a member of the neurotrophin growth factor family. A single-nucleotide polymorphism (SNP) has been identified in the human BDNF gene, which results in a single-nucleotide substitution that leads to an amino acid change from valine to methionine in position 66 (Val66Met) leading to an impaired intracellular trafficking and decreased depolarization and secretion of BDNF [1]. In Multiple Sclerosis (MS), the polymorphism Val66Met has been correlated with alteration of cognitive performance and measures of brain atrophy [2], with ambiguous results. Evidence is accumulating that there is an involvement of DNA methylation in the regulation of BDNF expression.
The aim of the present study was to assess in blood samples of MS patients the potential correlation between methylation status of CpG site near BDNF-Val66Met polymorphism and the severity or progression of the disease, aiming at using the methylation of this site as a biomarker of the disease progression.

METHODS

We recruited 209 MS patients (130 women and 79 men) with mean age 45,9 ± 12,7 years. The mean duration of follow-up (equivalent to illness duration) was of 13.4 years (SD=8.2; median=12 years; maximum=37 years); mean age of onset was 32.5 years (SD=11.6; median=32). The MS patients included in this study were genotyped for the BDNF Val66Met polymorphism at nucleotide 196 (G/A) using a high resolution melt analysis [3]. For each patient we quantitatively measured the methylation level of cytosine included in the exonic CpG site that can be created or abolished by the Val66Met BDNF polymorphism.
Furthermore we analyzed the clinical history of each patient and determined the time elapsed since the onset of the disease and an EDSS score of 6.0.

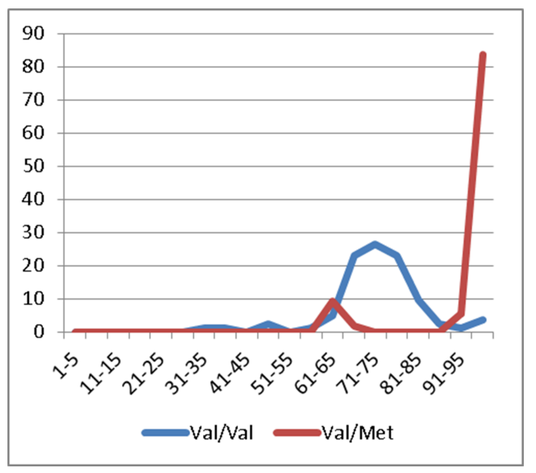

Figure 1: distribution of the percentage of methylation of BDNF gene in Val/Val patients (blue) and Val/Met patients (red)

RESULTS

The genetic analysis identified 122 subjects (58.4% of total sample) carrying the Val/Val genotype, 81 subjects (38.8%) with Val/Met genotype, and 6 patients (2.8%) carrying the Met/Met genotype. We found that the majority of the Val/Val patients had a methylation level between 60% and 90%, while the majority of the Val/Met population had a methylation level above 90% (p<0,001) (Figure 1).
When the endpoint of an EDSS score of 6 was taken into account by means of a survival analysis, 52 failures (i.e., reaching an EDSS score of 6) were reported. As shown (Figure 2), the failure rate was evenly distributed in the patients carrying or not carrying the Met allele (exposed=Met+; IRD=-0.009; 95% confidence interval [95%CI]=-0.0200-0.0014; p=0.102). When the sample was stratified according to the percentage of the BDNF methylation, subjects falling below the median (median methylation=81%) were at higher risk of failure (IRD=0.016; 95%CI=0.0050-0.0279; p=0.004). Figure 3 displays the survival estimates of the sample stratified according to BDNF gene percentage of methylation.

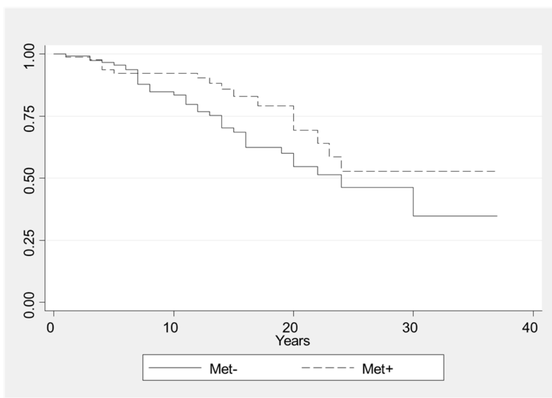

Figure 2: survival estimates of subjects carrying (Met+) or not carrying (Met-) the Met allele of the BDNF gene polymorphism

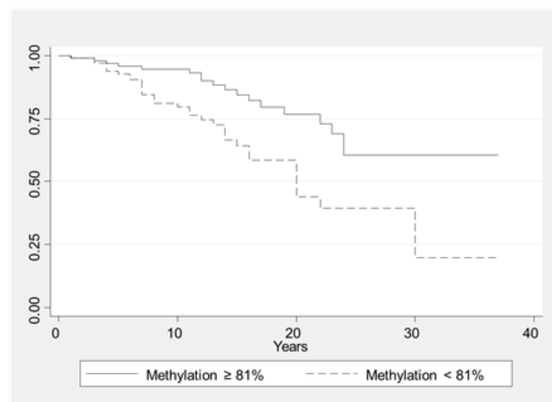

Figure 3:survival estimates of subjects with BDNF gene methylation above or below the median (81%)

CONCLUSIONS

The reduction of BDNF gene methylation could be seen as a protection mechanism for the brain. In patients with high disease progression the hypomethylation of the BDNF gene could increase the secretion of the protective neurotrophin. Moreover, with the increasing of the age, a progressive decrease of the brain functional reserve also occurs. So epigenetic modifications, as hypomethylation of the BDNF gene, could be an organism response to limit the brain functional reserve loss. Our study suggests that the **percentage of methylation of the BDNF gene could be used as a prognostic factor for disease progression toward a high disability in MS patient.**

REFERENCES

1. Chen ZY, Patel PD, Sant G, et al. Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and corticalneurons. J Neurosci. 2004 24: 4401-4411
2. Pezawas L, Verchinski BA, Mattay VS, et al. The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. J Neurosci. 2004 24: 10099-10102.
3. Tucker EJ, Huynh BL. Genotyping by high-resolution melting analysis. Methods Ml Biol 2014;1145:59-66

XLVII CONGRESSO NAZIONALE
22-25 OTTOBRE 2016 – VENEZIA