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Pilot Prospective Study on BDNF (Brain Derived Neurotrophic Factor) as a Predictive Biomarker of the Occurrence of PTSD (Post Traumatic Stress Disorder)

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Abstract: The pilot study's main objective was to assess the rate of serum BDNF (brain derived neurotrophic factor) and initial clinical course during three months of the matter submitted to a potentially traumatic event. In this study, 12 volunteers were recruited, 7 have been exposed to a traumatic event and 5 negative controls without psycho-trauma history. This study showed the following results: the rate of BDNF was significantly lower in the group of volunteers exposed to trauma compared with the control group: 6.20 ± 1.73 ng/mL for the group with trauma *versus* 21.79 ± 1.76 ng/mL for the control group with $P < 0.001$. The rate of serum BDNF is significantly collapsed in victims of physical aggression compared to those who have witnessed a traumatic event: 4.36 ± 0.37 ng/mL for assault group *versus* 6.94 ± 1.44 ng/mL control group event with $P = 0.03$. The level of BDNF is significantly inversely correlated with the intensity of the Peritraumatic distress ($r = -0.75$, $P < 0.05$). The rate of serum BDNF was significantly lower in the group with acute PTSD compared to group with no PTSD: 7.5 ± 0.9 ng/mL in the absence of PTSD ($n = 4$) *versus* 4.5 ± 0.49 ng/mL in the presence of PTSD ($n = 3$), $P = 0.001$.

Key words: Post traumatic stress, PTSD, brain-derived neurotrophic factor, BDNF, biomarker.

1. Introduction

The term PTSD (post traumatic stress disorder) was introduced in 1980 at the Third revision of the DSM [1]. It has undergone some changes in the DSM-III and DSM IV-R versions developed successively in 1987 and 1994 [2-3]. On the other hand, the "Acute Stress Disorders" diagnosis backwards from the 2nd day was added to it in the 1994 version DMS IV. This pathology appears in the 10th revision of International Classification of mental illness from 1992 [4]. Although significant progress has been made in terms of the diagnostic and therapeutic management, the fact remains that internationally, dramas supposedly related to the state of post traumatic stress still not resolved. These tragedies highlight that still remain some unknowns regarding prognostic factors to identify the victims exposed to a traumatic event. While it is estimated during life, 51% to 83% of the general population will be confronted with a traumatic event [5]. Some of the victims will develop a state of PTSD. The prevalence of PTSD differs considerably from one study to another: from 1 to about 10% probably due to the societal and cultural environment [6]. Indeed, first in the West countries, sexual assaults take first place, while traumatic event remains taboo and hidden in Asian region and other societies. Nevertheless, some authors question the validity of the diagnosis of PTSD based on several combinations of symptoms from a list of diagnostic criteria for DSM IV-R [7-8]. According to these authors, the diagnosis of PTSD would be unreliable because it is based on subjective clinical criteria that occurred after exposure to an often unverifiable psycho-traumatic potential events

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reported by patients including research of secondary benefits [9].

The research for a biological indicator is a key objective evidence to verify the reality of post-traumatic stress and screening of individuals at risk in order to focus the resources used in providing the victim with a decision more effective, comprehensive and early treatment to prevent or limit the progression to PTSD. However, until now vulnerability and protective factors are only partially identified. One of these protective factors is BDNF that is a neurotrophin belonging to the family comprising the neurotrophin NGF (nerve growth factor) and the neurotrophins NT3, NT4/5, NT6 and NT7 [10]. The major roles include regulation of BDNF activity through both the synapse plasticity facilitating synaptic transmission [11-12] and the trophicity acting as a promoter of the survival of neuronal populations during development and in adults and remodelling of neuronal populations factor [13-14].

In addition, the BDNF seems to be a potential biological indicator of PTSD [15]. The purpose of the present article is to quantify the concentration of serum BDNF in a group of victims in the early stages and follow clinically for 3 months in order to test the predictive power of BDNF versus the developed PTSD.

2. Experimental Procedures

Twelve volunteers were enrolled in this prospective study; divided into two groups: (1) 7 subjects have recently been exposed to a traumatic event (within 72h), and have felt intense fear, helplessness, or horror; (2) 5 subjects without trauma exposure as control group.

Excluded were those neurological illness; psychiatric disorders, alcohol or substance abuse or dependence, and serious medical illnesses, including cardiovascular, gastrointestinal, respiratory, endocrinologic, and genitourinary system diseases. They were not taking an anti-inflammatory medication during the previous two weeks. Some confounders of serum BDNF such as smoking and obesity are not included in this study. Effectively, these situations can interfere with the findings. All subjects included provided written informed consent, after receiving a complete description of the study and having the opportunity to ask questions.

The psychiatric assessments included: the THQ (Trauma History Questionnaire) at day 1, PDI (Peritraumatic Distress Inventory) at day 1, PDEQ (Peritraumatic Dissociative Experiences Questionnaire) at day 1, SCID-I (Structured Clinical Interview for DSM-IV Axis I Disorders) at day 30 and day 90; PCL-S (PTSD CheckList-Specific) at day 30 and day 90.

The Venous blood was collected between 8 and 9 a.m. and centrifuged within 20 min after sampling at 2000 × g for 20 min then aliquoted and stored at -80 °C until analysis. Serum BDNF was quantified by ELISA (RayBio™ technique). BDNF assay employed an antibody specific for human BDNF coated on a 96-well plate. Cortisol concentration dosage was obtained by Electro-ChemiLuminescence immunoassay method (Cobas™, Roche Laoratories).

The statistical analysis (Student's test and Pearson's correlation coefficients) were carried out by Microsoft Excel 2013™.

3. Results

In this study, 12 volunteers have been selected: 7 (5 men and 2 women) aged 34 ± 13.4 years have been exposed to a traumatic event and 5 negative controls (3 men and 2 women) aged 44 ± 14.2 years were without psycho-trauma history (Table 1 and Table 2). 2 volunteers were subjected to severe physical abuse and five witnesses hanging or fatal injury. The time between exposure to the traumatic event and the consultation and therefore the collection of the blood sample for analysis including serum BDNF and serum cortisol collected between 2 h and 72 h.

3.1 Comparison of Serum Levels of BDNF and Cortisol

In the general population (exposed and unexposed, *n*

Table 1 Characteristics of the group of volunteers exposed to trauma.

Subject	Gender	Age (years)	Nature of the event	Delay* (h)	BDNF (ng/mL)	Cortisol (µg/dL)
V-1	F	45	Physical assault	18	4.62	Not measured
V-2	M	23	Physical assault	72	4.09	8.35
V-3	F	23	Witness hanging	72	6.99	6.04
V-4	F	47	Witness hanging	72	8.61	14.82
V-5	M	28	Witness of fatal injury	72	6.58	13.67
V-6	F	20	Witness of fatal injury	72	7.76	11.27
V-7	F	52	Witness hanging	2	4.78	39.12
Average		34.00		54.29	6.20	15.55
Standard deviation		13.47		30.60	1.73	12.00

*Delay: time between trauma event and blood collect.

Table 2 Characteristics of control group.

Subject	Gender	Age(years)	BDNF(ng/mL)	Cortisol(µg/dL)
W-1	M	40	19.48	Not measured
W-2	M	55	22.79	8.89
W-3	F	53	23.19	7.21
W-4	F	21	20.31	31.47
W-5	M	52	23.19	10.08
Average		44.2	21.79	14.41
Standard deviation		14.24	1.76	11.43

= 12), the average rate of serum cortisol and serum BDNF were estimated respectively at 15.09 ± 11.13 µg/dL (for cortisol, n = 10) and 12.70 ± 8.20 ng/ml (for BDNF, n = 12). There is no correlation between the both levels of BDNF and cortisol.

There is no significant difference between the cortisol group "exposed to a traumatic event" *versus* "unexposed" negative control group: level's group exposed showed an average value of 15.55 ± 10.95 µg/dL *versus* 14.41 ± 11.43 µg/dL for the unexposed group.

3.2 BDNF Levels and Nature of the Traumatic Event

The serum BDNF levels are significantly lower in volunteers exposed to trauma compared with the control group (Fig. 1): 6.20 ± 1.73 ng/mL for the group with trauma *versus* 21.79 ± 1.76 ng/mL for the control group (witnesses), with $P < 0.001$.

There is no correlation between BDNF levels and age of the subject. There is no correlation between BDNF levels and the delay between exposure to the event and the BDNF sampling (this period ranged from 2h to 72h) (see Table 1).

The values of serum BDNF women are not significantly different from those for men: the average of BDNF level for men is 5.34 ± 2.67 ng/mL *versus* 6.55 ± 1.48 ng/mL for women.

The BDNF levels were significantly lower in the group of victims of physical aggression compared to the group who have witnessed traumatic event: 4.36 ± 0.37 ng/mL for assault group (n = 2) *versus* 6.94 ± 1.44 ng/mL for control group event and P = 0.03 (n = 5) (see Fig. 2).

3.3 BDNF and Peritraumatic Reactions

Table 3 shows the questionnaire results of PDEQ (Peritraumatic dissociative experiences) and DPI (Inventory of peritraumatic distress disorder).

3.3.1 Peritraumatic Dissociative Experiences and BDNF

The score of PDEQ was estimated at 29.25/50 (29.25 ± 12.31) with a minimum of 14/50 and a maximum of 46/50 (see Table 3). There is no correlation between BDNF levels and PDEQ's score.

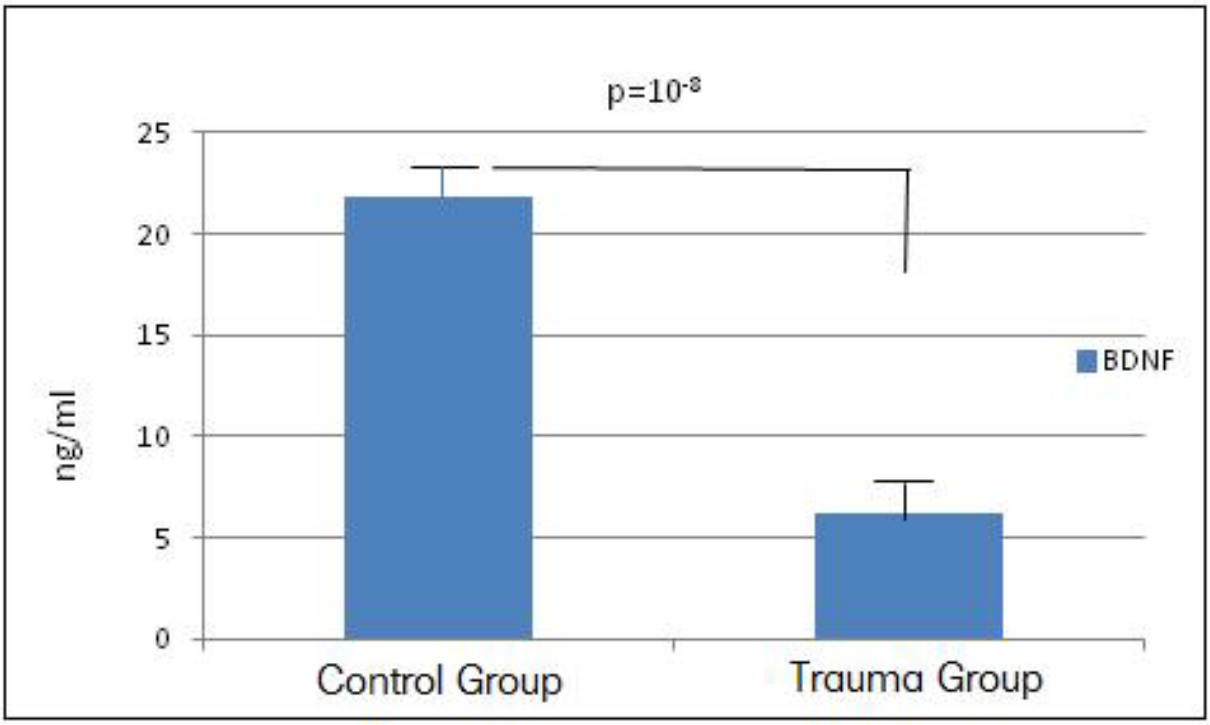

Fig. 1 Comparison of BDNF rate between the victims and control group.

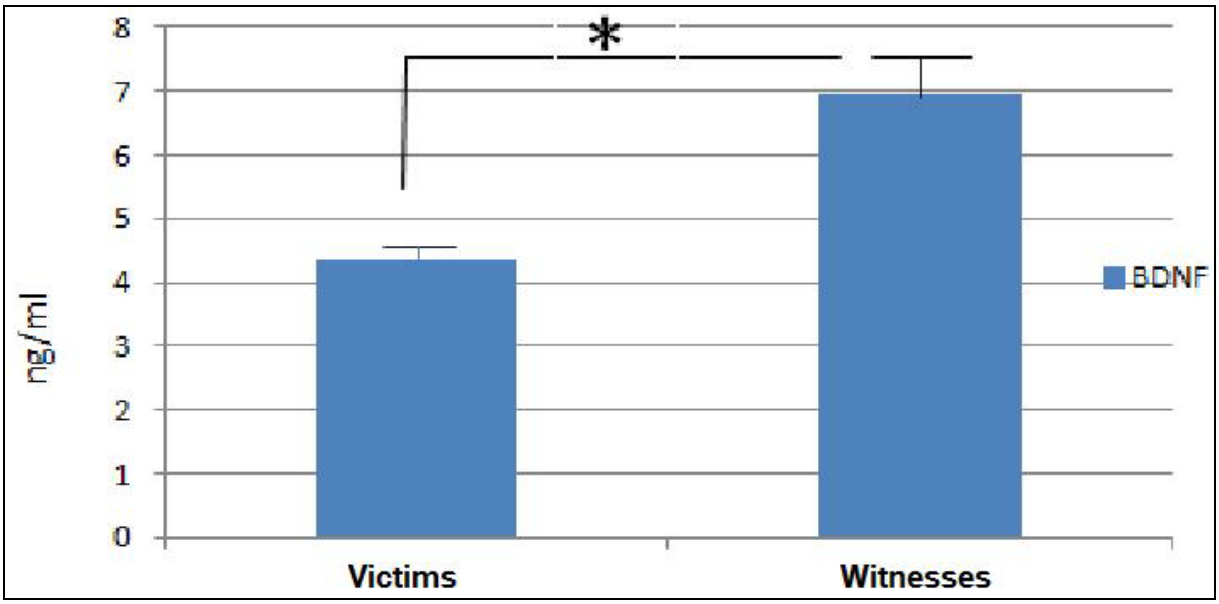

Fig. 2 Comparison of BDNF rate between victims and witnesses of trauma event.

3.3.2 BDNF and Peritraumatic Distress

The average score of the DPI was estimated at 26.87/52 (26.87 ± 11.70) with a minimum of 8/52 and a maximum of 43/52. There is a good correlation between the rate of BDNF and PDI score ($r = -0.74$, $P < 0.05$). These results support our hypothesis: the severity of post-traumatic distress is inversely proportional to the rate of BDNF.

The BDNF levels are lower in the presence of symptoms in all peritraumatic distress items with the exception of Item 7 “I was worried for the safety of others” (Fig. 3).

Table 3 Comparison between the levels of BDNF and scores of questionnaires peritraumatic dissociative experiences (Peritraumatic Dissociative Experiences Questionnaire, PDEQ) and Inventory of peritraumatic stress disorder (Peritraumatic Distress Inventory, PDI).

Subject	BDNF (ng/mL)	PDEQ	DPI
V-01	4.62	41	35
V-2	4.09	42	43
V-03	6.99	46	32
V-04	8.61	28	18
V-05	6.58	14	8
V-06	7.76	17	16
V-07	4.78	20	33
Average	6.20	29.25	26.43
Standard deviation	1.73	12.31	12.53

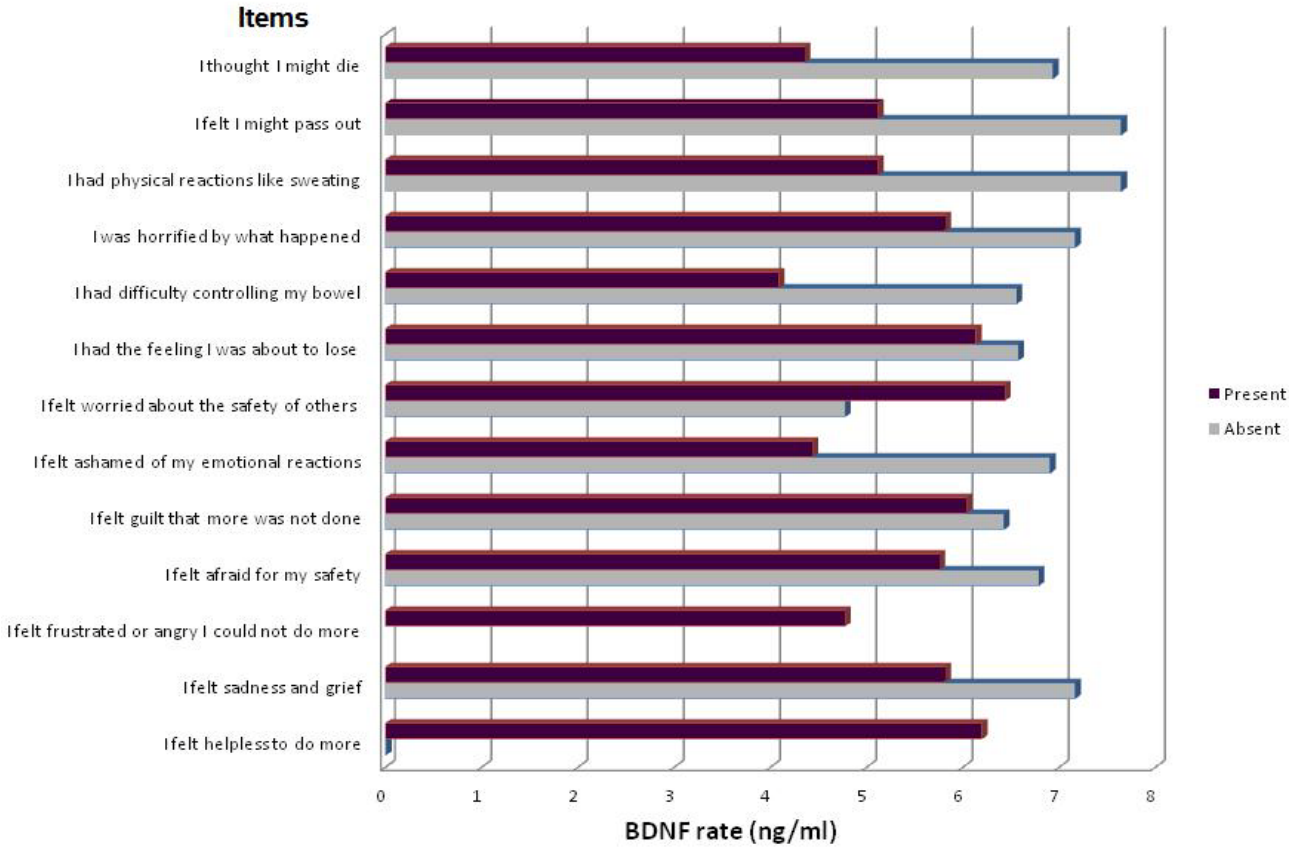

Fig. 3 Comparison of BDNF rate between BDNF levels and clinical symptoms of DPI.

3.3.3 BDNF Rate and Diagnosis of PTSD in the First Month

Based on SCID-I (Structured Clinical Interview for DSM-IV Axis I Disorders), the diagnosis of PTSD was selected in 3 cases. The average concentration of BDNF was significantly higher in the absence of PTSD: 7.5 ± 0.9 ng/mL in the absence of PTSD (n = 4) *versus* 4.5 ± 0.4 ng/mL in the presence of PTSD (n = 3), P = 0.001 (Fig. 4).

3.3.4 BDNF Rate and Diagnosis of PTSD in the Third Month

The diagnosis of PTSD was retained in one case. In the absence of PTSD, the mean concentration was 6.44 ± 1.41 ng/mL. In the presence of PTSD, the average serum BDNF becomes 4.78 ng/mL and it's statistically different.

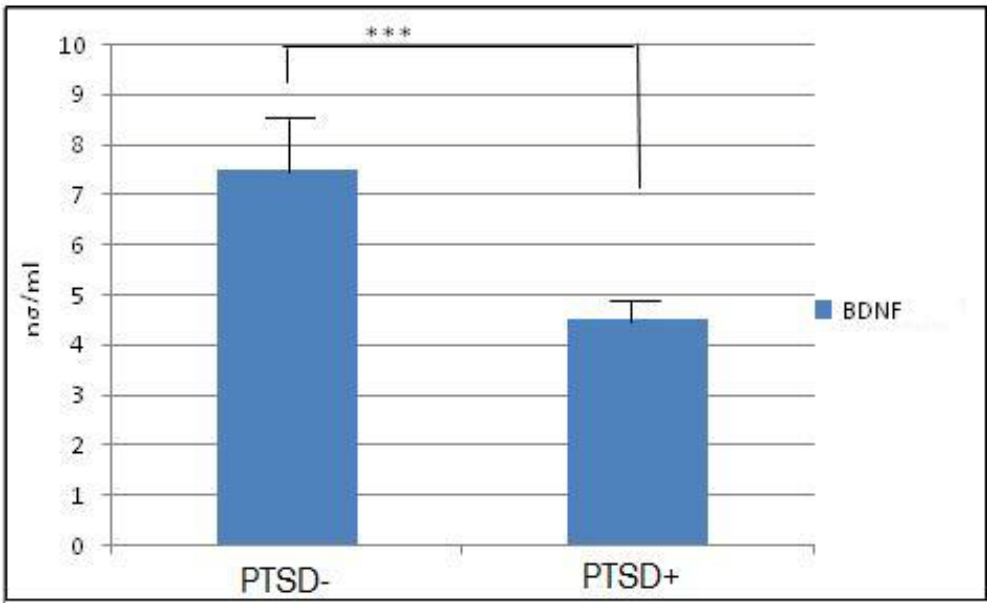

Fig. 4 Comparison of BDNF in the presence versus absence of PTSD in the first month rate.

Table 4 Comparison between the levels of BDNF and PTSD Checklist scores questionnaires-specific (PCL-S) on the first month (PCLS30) and 3rd month (PCLS90).

	BDNF (ng/mL)	Scores PCLS30	Scores PCLS90
V-01	4.62	37	33
V-2	4.09	27	0
V-03	6.99	14	7
V-05	8.61	12	2
V-06	6.58	0	0
V-07	7.76	9	3
V-08	4.78	33	4
Average	6.20	22.76	7.01
Standard deviation	1.73	16.74	11.70

3.3.5 Confrontation of BDNF Levels and Symptoms of PTSD

Table 4 shows the scores of questionnaires PCL-S (PTSD Checklist-Specific) at the first month (PCLS30) and at the 3rd month (PCLS90).

The average score PCL30 is estimated at 22.76/68 (22.76 ± 16.74) with a minimum of 0/50 and a maximum of 37/50. There was a good correlation between the BDNF level and the PCL30 score ($r = -0.77$, $P < 0.05$). The severity of PTSD symptoms is inversely proportional to the levels of BDNF in the peritraumatic period.

The average score PCL90 is estimated at 13.51/68 (13.51 ± 21.01) with minimum of 0/50 and a maximum of 35/50. There is no correlation between the BDNF level and the PCL90 score ($r = 0.36$, NS).

In general, the levels of BDNF is higher each time when the PCLS is absent in the symptom list.

4. Discussion

In another pilot study, we showed that there is a good correlation between blood and CSF BDNF levels [16]. The CSF sampling is difficult to obtain in routine and the serum is a good alternative for sampling. The limit of our study is the small size of patients. We consider that this study is a pilot and prospective approach to test the serum BDNF as biomarker for trauma events. A new study with a great number of patients is necessary to confirm our finding. The inclusion of such patient is difficult because of the multiple reasons of exclusion

states (obesity, smoking, psychiatric disorder…).

In this study, there is no correlation between circulating levels of cortisol and BDNF.

The BDNF levels were significantly lower in the group of volunteers exposed to trauma compared with the control group: 6.20 ± 1.73 ng/mL for the group with trauma *versus* 21.79 ± 1.76 ng / ml for control group. The same rate is significantly collapsed in victims of physical aggression compared to those who have witnessed a traumatic event: 4.36 ± 0.37 ng/mL for assault group *versus* 6.94 ±1.44 ng/mL for control group event with $P = 0.03$. The peritraumatic reactions were explored via questionnaires "PDEQ" and "PDI" during the visit of inclusion.

The level of BDNF is not significantly correlated with the intensity of dissociation of peritraumatic reactions. But so far the immediate effects peritraumatic dissociation is discussed as well as some authors [17-18]. The peritraumatic dissociation can protect the individual from intense emotions such as feelings of fear, helplessness and horror. However, the peritraumatic dissociation would increase the risk of developing PTSD [19].

As against the BDNF levels were significantly inversely correlated with the score of the inventory of peritraumatic stress (DPI) with r = -0.75, $P < 0.05$. Thus a diminution of BDNF levels is observed whenever distress symptom is present with the exception of the item 7 in relation to the other concern. The increase in BDNF seems to be related to the concern for others, while the "collapse on itself" would lead to the collapse of this neurotrophin.

According SCID-I (Structured Clinical Interview for DSM-IV Axis I Disorders), 3 patients had PTSD at the end of the first month of which continued after the third month. Hence the establishment of diagnosis according to the criteria DSM-IV-R 3 cases of acute PTSD (1 month < symptom duration < 3 months) and 1 chronic PTSD (symptom duration > 3 months).

The BDNF levels were significantly lower in the group with acute PTSD compared to the group with no PTSD: 7.5 ± 0.9 ng/mL in the absence of PTSD ($n = 4$) *versus* 4.5 ± 0.4 ng/mL in the presence of PTSD ($n = 3$), $P = 0.001$.

Similarly, the levels of BDNF in the presence of only one case of chronic PTSD in 4.78 ng/mL was outside the 95% confidence interval concentrations of BDNF group of people free of chronic PTSD (from 5.03 to 7.86 ng/mL). The BDNF values found in volunteers exposed to a traumatic event match those that have been reported by the team that found (Dell'Osso et al., 2009) are similar to the BDNF values in people suffering from PTSD (5.3 ± 1.1 ng/mL).

Finally, although this study involved only a small sample of volunteers ($n = 7$), the results highlight the importance of BDNF assay to better target victims at high risk of developing PTSD and what outperformed the support. A prospective study with more volunteers is in progress to confirm the results of this pilot study.

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