

Brain - Derived Neurotrophic Factor - a Marker for the Balneal Treatment of Chronic Low Back Pain?

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Up till now, to our knowledge, there are no studies evaluating serum Brain - Derived Neurotrophic Factor (BDNF) levels in patients with degenerative chronic low back pain under rehabilitation treatment. BDNF is a neuroprotein associated with neuropathic pain and represents an important mediator of the effects of physical exercise. Complex balneal treatment with hot Techirghiol sapropelic mud reduces pain and increases serum levels of BDNF in these patients.

Key words: degenerative pain, BDNF, balneal, sapropelic mud

The main cause of low back pain (LBP) worldwide is lumbar disc herniation (LDH). LDH, a degenerative disease which induces narrowing of the spinal canal, seems to be associated with several single nucleotide polymorphisms (SNPs). For example, seven SNPs were genotyped in a Chinese study performed over 1072 patients [1] and a relation was found between these SNPs and brain derived neurotrophic factors (BDNFs) and their genes (BDNFs).

BDNF is part of the neurotrophin family of growth factors. They are related to the canonical nerve growth factor, playing an important role in the maturation and differentiation of neurons. Low levels of BDNF are associated with neurodegenerative disorders as Parkinson's disease, multiple sclerosis or Alzheimer disease [2]. Data in medical literature related to BDNF level and its involvement in LBP is controversial, some studies revealing elevated levels of BDNF after pain-relieving methods of physical therapy [3], some others: high levels of plasma BDNF in old women with LBP compared to pain-free controls [4].

Considering the growing burden of LBP worldwide, the studies over how balneal treatment affects neurotrophic factors involved in neural regeneration and protection after spinal cord injury or peripheral nerve disorders can represent the beginning of a new approach in rehabilitation and non-pharmacological therapies [5, 6]. Under these circumstances, we consider our study over the serum level of BDNF in patients treated for LBP with sapropelic mud from Techirghiol lake to be important and proving that balneal treatment significantly modifies the serum level of BDNF.

Experimental part

We present a prospective case-control cohort study, which included 50 patients hospitalized for 2 weeks in the Balneal and Rehabilitation Sanatorium of Techirghiol (BRST). Patients signed an informed consent and the study was approved by the ethical committee of the Sanatorium. Patients with degenerative chronic LBP, with indications for balneal treatment, both women and men, were included

in the study. Exclusion criteria were: any inflammatory diseases, high blood pressure, cardiac failure, any pulmonary, renal, endocrine, neurologic or oncologic diseases, skin lesions, any antidepressant treatments. Patients were divided into two groups: hot mud bath group (HMBG) and a statistically matched control group (CG). Patients in the first group benefited from hot mud baths treatment and complex rehabilitation treatment such as electrotherapy, kinetotherapy and massage therapy. The control group had the same treatment, except for the hot mud baths. Each patient was clinically tested before and after treatment. Schober index, finger ground distance (IDS) index (for evaluation of lumbar spine mobility) and the visual analogue scale (VAS) for evaluation of pain were monitored. For each patient blood samples were collected in the beginning and in the end of treatment in order to determine the BDNF serum levels. For quantitative detection of BDNF we used a sandwich high sensitivity Eliza kit: Human BDNF PicoKine form Booster Biologic Technology (USA) and Eliza reader StatFax 4700 Microstrip Reader Awareness Technology (USA). Blood prelevation was performed in the same conditions for every patient and laboratory testing was performed by the same doctor. Patients completed a demographic questionnaire regarding age, gender, residence, personal history of pain, body mass index (BMI), frequency of treatment in BRST (twice a year, as indicated, once a year, sporadically and for the first time). Hot mud bath therapy involved diluting 10-15 kg of sapropelic mud, from Techirghiol Lake, in a water tub. The patient was immersed in the hot mud bath for 20 minutes, at 38-39°C under supervision of a physiotherapist.

Statistical evaluation of obtained data was performed using Wilcoxon test (level of significance: 0.05) for dependent samples, the nonparametric Mann-Whitney U test (level of significance: 0.05) for independent samples. Chi-Square test (with $p < \alpha = 0.05$ level of significance) and Spearman's rho were also used. Minimum, maximal, median and Interquartile Range values were obtained and compared.

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Results and discussions

Most of our patients were women, the median age, in both groups, was 54 years old and the majority of the patients included in the study were overweight and had urban residence.

The demographic features of our groups are detailed in Table 1.

We evaluated VAS scores at admission and discharge for each patient and we discovered significant lower VAS values at discharge than VAS values at admission. (Figure 1).

The Wilcoxon test confirmed statistically significant differences of VAS median values before and after treatment for CG ($p < 0.001$) and for HMBG ($p < 0.0001$), (Table 2).

The result of Wilcoxon test for Schober test values in HMBG patients confirmed statistically significant differences between the median values at admission and those at discharge $p < 0.001$ (Table 3). Analyzing the *finger*

–*ground index* for both groups at admission and discharge, we did not find any statistically significant differences (Table 3).

We evaluated BDNF serum levels for each patient at admission and at discharge (Table 4).

According to the non-parametric Mann-Whitney U test there were no significant differences between serum BDNF values of the two groups at admission ($p = 0.123 > 0.05$) while at discharge the values significantly differed between groups ($p < 0.001$) (Figure 3). In the same time the Wilcoxon test confirmed that within each group the values of serum BDNF at discharge were significantly different from the ones at admission ($p < 0.001$) (Figure 3).

According to Box-Plot representation (Figure 3) the BDNF values in control group were higher at admission than at discharge, while in HMBG the BDNF values were higher at discharge than at admission. We did not find any correlation between BDNF serum values and regular (once or twice per year) or sporadic balneal treatment. We did not discover any significant correlation of serum BDNF

		Hot Mud Bath Group	Control Group
Number		25	25
Age (years)		54.00±9.147 (39-68)	54.00±6.813 (41-67)
Gender	Male	7	10
	Female	18	15
BMI (Kg/m ²)	18.50-24.99	9	15
	25-29.99	8	5
	30-34.99	5	2
	35-39.99	2	3
	≥40	1	0
Urban Residence		88% (22)	92% (23)
Frequency of balneal treatment:	biannual	12%	8%
	annual	48%	24%
	occasional	20%	32%
	First time	20%	36%
VAS score at admission		7.08±1.63	5.28±1.99
Quantified Schober index at admission		4.76±0.72	4.68±0.90

BMI=body mass index, VAS=visual analogue scale

Table 1
DEMOGRAPHIC FEATURES OF BOTH GROUPS

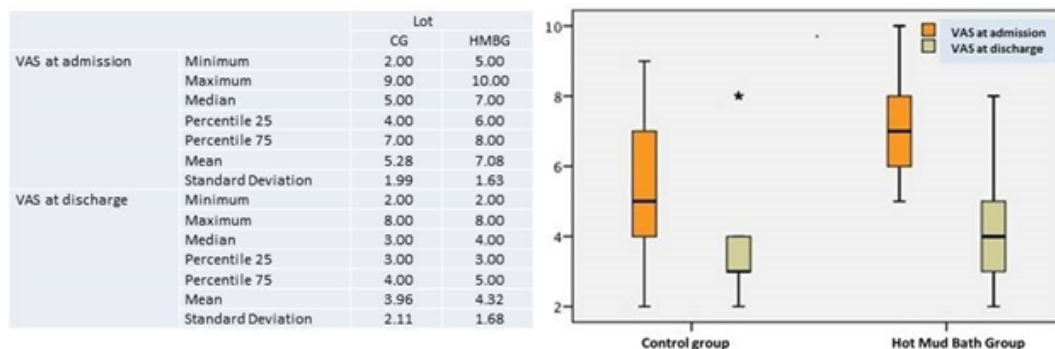


Fig. 1. VAS scores distribution for patients from the study groups and Box-Plot representation of VAS scores at admission/discharge for each of the studied groups.

	Group			VAS at admission	VAS at discharge
Spearman's rho	Control group	VAS at admission	Correlation Coefficient	1.000	.571**
			Sig. (2-tailed)	.	.003
			N	25	25
		VAS at discharge	Correlation Coefficient	.571**	1.000
			Sig. (2-tailed)	.003	.
			N	25	25
	HMBG	VAS at admission	Correlation Coefficient	1.000	.823**
			Sig. (2-tailed)	.	.000
			N	25	25
		VAS at discharge	Correlation Coefficient	.823**	1.000
Sig. (2-tailed)			.000	.	
N			25	25	

** Correlation is significant at the 0.01 level (2-tailed).

Table 2
SIGNIFICANCE OF VAS VARIATIONS

Table 3
SPEARMAN'S RHO, SIGNIFICANCE OF SCHOBER'S TEST AND FINGER-GROUND INDEX VARIATIONS

			Schober at admission	Schober at discharge			"Finger – ground index" at admission	"Finger – ground index" at discharge
Control Group	Schober at admission	Correlation Coefficient	1.000	.787**	"Finger – ground index" at admission	Correlation Coefficient	1.000	.999
		Sig. (2-tailed)	.	.000		Sig. (2-tailed)	.	.000
		N	25	25		N	25	25
	Schober at discharge	Correlation Coefficient	.787**	1.000	"Finger – ground index" at discharge	Correlation Coefficient	.999**	1.000
		Sig. (2-tailed)	.000	.		Sig. (2-tailed)	.000	.
		N	25	25		N	25	25
	Schober at admission	Correlation Coefficient	1.000	.526**	"Finger – ground index" at admission	Correlation Coefficient	1.000	.958**
		Sig. (2-tailed)	.	.007		Sig. (2-tailed)	.	.000
		N	25	25		N	25	25
Hot Mud Bath Group	Schober at admission	Correlation Coefficient	1.000	.526**	"Finger – ground index" at admission	Correlation Coefficient	1.000	.958**
		Sig. (2-tailed)	.	.007		Sig. (2-tailed)	.	.000
		N	25	25		N	25	25
	Schober at discharge	Correlation Coefficient	.526**	1.000	"Finger – ground index" at discharge	Correlation Coefficient	.958**	1.000
		Sig. (2-tailed)	.007	.		Sig. (2-tailed)	.000	.
		N	25	25		N	25	25

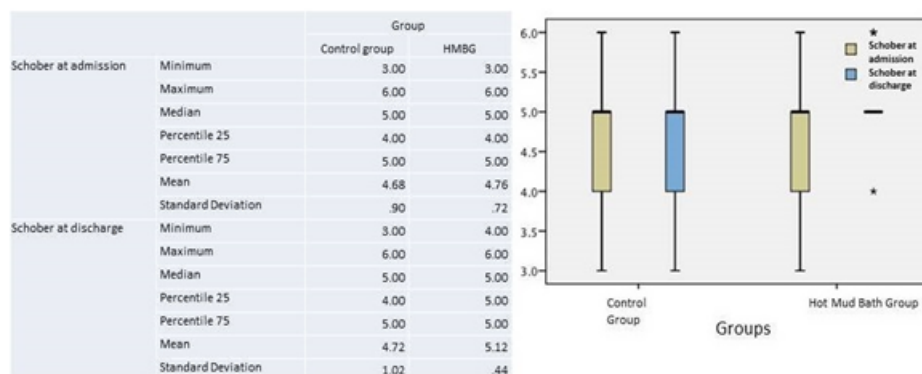
** . Correlation is significant at the 0.01 level (2-tailed).

	Group			
	Control Group		HMBG	
	BDNF at admission (pg/mL)	BDNF at discharge (pg/mL)	BDNF at admission (pg/mL)	BDNF at discharge (pg/mL)
Minimum	318.90	39.50	346.00	1016.80
Maximum	1842.00	1698.00	1649.20	1998.00
Median	1416.00	498.70	1211.40	1646.70
Percentile 25	690.00	272.20	1051.00	1402.40
Percentile 75	1771.00	986.40	1304.00	1846.50
Mean	1257.56	654.44	1147.56	1629.97
Standard Deviation	528.23	504.77	316.67	266.69

Table 4
LEVELS OF SERUM BDNF IN CONTROL GROUP AND HOT MUD BATH GROUP

with gender or age, with the exception of CG where the older the patient the lower the BDNF at discharge ($p < 0.001$) (Table 5).

Chronic LBP represents a major health problem [7-9] and diverse treatments in order to reduce pain and disability are experimented [10]. BDNF, a neuroprotein associated



Fi. 2. Schober index distribution for patients from the study groups and Box-Plot representation of Schober index quantified scores at admission/discharge for each of the studied groups.

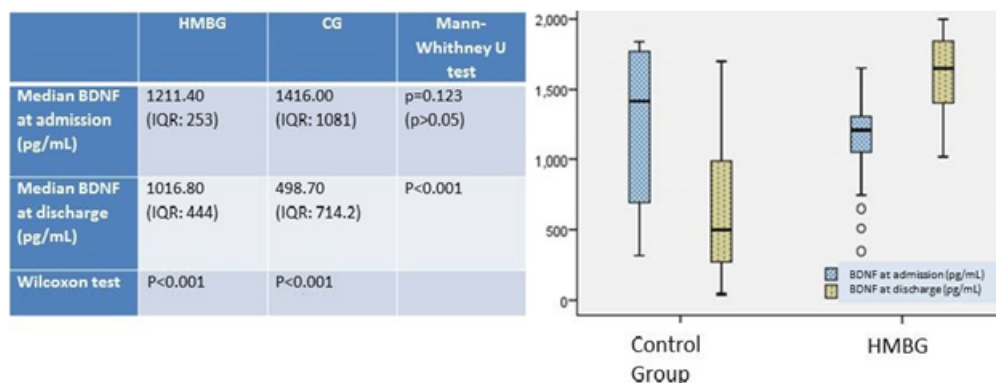


Fig. 3. Statistical evaluation for serum BDNF within each group and between groups both at admission and at discharge and Blox Plot representation of BDNF values of each group at admission and at discharge

HMBG		BDNF at discharge pg/ml	Patient's age
Spearman's rBDNF at discharge pg	Correlation Coefficient	1.000	-.012
	Sig. (2-tailed)	.	.953
	N	25	25
Age	Correlation Coefficient	-.012	1.000
	Sig. (2-tailed)	.953	.
	N	25	25
Control Group		BDNF at discharge pg/ml	Patient's age
Spearman's rBDNF at discharge pg	Correlation Coefficient	1.000	-.657**
	Sig. (2-tailed)	.	.000
	N	25	25
Age	Correlation Coefficient	-.657**	1.000
	Sig. (2-tailed)	.000	.
	N	25	25

** . Correlation is significant at the 0.01 level (2-tailed).

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Table 5
AGE CORRELATION WITH BDNF AT DISCHARGE IS SIGNIFICANT ONLY IN CG

with neuropathic pain and mediator of the effects of physical exercise [11, 12], has been extensively studied in recent years, especially regarding the influence of exercise on chronic LBP [13]. The patients in our study had a complex treatment (including hot mud baths) for chronic LBP and we searched if serum levels of BDNF are influenced by this kind of treatment.

Overweight and obesity are reported as risk factors for chronic LBP [6, 9] and analyzing the features of our patients we discovered that less than half of our patients had a normal weight. Obesity itself was found to associate with low levels of BDNF especially in patients with mutations of the gene encoding its receptor - tyrosine kinase receptor type 2 (Ntrk2) [14]. This situation was described especially in children with obesity and psychomotor retardation, as in Biddle-Bardet syndrome [14, 15]. But, despite our expectations, we did not find any significant correlation between BDNF and BMI. This comes in concordance with a similar meta-analysis performed by Sandrini L and colab. in 2018 [16]. We did not find any correlation between serum levels of BDNF and the periodicity of balneal treatment, either.

As women were the majority of our patients, we take into account a future extension of our study, considering

the relation between balneal treatment, the levels of serum BDNF and gynecological pathology. A study from Wessels J.M.et al. identified prominent BDNF and Ntrk2 isoforms in the human uterine muscle and endometrium [17]. As magnesium administration induces an increase in BDNF level [17] but also inhibits uterine muscle contraction [18] a possible relation can be found between the two mechanisms involved in uterine relaxation, with possible therapeutic consequences. Another possible future question could be, in this context, if pain decrease could be related also on uterine BDNF-calcium effect, superposed on the known calcium actions on the myometrium [19, 20].

Endometriosis, a benign disease represented by existence of endometrial tissue outside the uterine cavity, is associated with important abdominal pain [21.], sometimes mistaken for LBP. A recent study [22] found that BDNF concentrations in serum and peritoneal fluid were significantly high in women with endometriosis with pain, suggesting that BDNF can play a role in pain's origin. Furthermore, women with endometriosis use physiotherapy and kinesiology in order to reduce pain [23].

VAS evaluation for both groups revealed statistically significant reduction of this parameter and this confirms

that rehabilitation treatment reduces pain [24, 25]. The possible explanation for the greater reduction of VAS score in CG than in HMBG after treatment results from the immediate short term pro-inflammatory effect induced by balneal treatment with sapropelic mud, inflammation that cease in several days from the balneal treatment. So, VAS score is expected to diminish after several days, also. Unfortunately, we did not have the possibility to reassess VAS score in patients from HMBG after discharge. Regarding Schober test we found statistically significant differences only for the patients from the HMBG. This demonstrates the improvement of flexibility of the lumbar spine segment after balneal treatment with hot sapropelic mud, as other studies have revealed [25].

We found that serum BDNF levels are significantly and reversely correlated with patients' age only in CG: the higher the age the lower the BDNF. As our groups did not differ significantly regarding age, perhaps this reduction is induced by balneal treatment without sapropelic mud administration. The result can be biased by the small number of patients included in the study. Statistically significant differences for serum levels of BDNF in both groups, at discharge, were found. Our results revealed a significant reduction in BDNF levels in CG and a statistically significant augmentation of BDNF levels in the HMBG patients. We do not have a clear explanation for the reduction of BDNF levels in CG, we can just suppose that the physical effort during kinetotherapy, even if aerobic, was not strong enough to induce a rise in BDNF level. We compared the results in our CG to other two studies in medical literature. One revealed that only high-intensity locomotor exercise increased the levels of serum BDNF compared to moderate intensity physical exercise in patients with incomplete spinal cord injuries who are not carriers of Val66Met single-nucleotide polymorphism [26] and in another one, in a meta-analysis over 29 studies regarding the effect of exercise training on resting levels of BDNF in peripheral blood, Dinoff A et al. found that aerobic but not resistance training increased blood BDNF levels [27]. In the meantime, the reduction in BDNF serum level in our CG comes in opposition with the results of a study in which aquatic physical therapy twice per week for 5 weeks increased the level of BDNF [3]. In another study, [4] the use of analgesic or antidepressant drugs induced a significant reduction of serum BDNF in old women after an acute episode of LBP. Extrapolating, we can consider that balneal therapy, without sapropelic mud, may have the same effect over serum BDNF levels. We did not find any medical data to compare with the increased levels of serum BDNF in our patients who received balneal treatment with sapropelic mud.

Conclusions

In our study, balneal therapy with Techirghiol sapropelic mud induced a significant elevation of serum BDNF levels, associated with significant pain reduction according to VAS score, and with a significant improvement in lumbar mobility as Schober's test revealed. As far as we know, up to this moment, there are no studies regarding BDNF serum levels in patients with degenerative chronic LBP under mud therapies, so we think that our study brings significant information in this field and it can represent the starting point for other similar studies over a bigger number of patients.

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