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RESEARCH ARTICLE

N-ACETYL-ASPARTATE AS AN EVALUATION METHOD FOR THE EFFECTIVENESS OF COGNITIVE REHABILITATION IN MILITARY PERSONNEL IN ACTIVE SERVICE WITH TRAUMATIC BRAIN DAMAGE

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ABSTRACT

Introduction: This research work, evaluated by means of magnetic resonance spectroscopy the response to treatment for 3 months with cognitive rehabilitation in those military personnel who are in the active service of the Navy of Mexico, and who during their activities performed by and during the time of service, they have suffered some kind of closed head injury and that from this they have had as a complication the development of mild cognitive deterioration, determining this event as traumatic brain injury, being of the utmost importance the evaluation of this pathology and his treatment because this can determine the improvement in his lifestyle and mental health of the military, his incorporation to the competent activities to the service or determine the need for retirement in a timely manner.

Objective: To determine the effectiveness of N-Acetyl-Aspartate as a method of evaluating treatment with cognitive rehabilitation, in active service soldiers with traumatic brain injury.

Material and methods: This work is a quasi-experimental analytical study, with pre-post intervention design or determined as a test of the usual clinical practice, in which the cognitive rehabilitation treatment in the active service military will be evaluated. who have suffered a traumatic brain injury and who, as a sequel, have had cognitive impairment.

Procedure: The response to treatment with the measurement of the metabolite N-Acetyl-Aspartate will be determined by means of magnetic resonance spectroscopy taken before the cognitive rehabilitation treatment and at the end of this, to establish if there were changes in the mild cognitive deterioration in a analysis both clinical and by image.

Statistical analysis: The evaluation of N-Acetyl-Aspartate was carried out by means of a statistical analysis with Student's T, finding that the differences between pre- and post-treatment were statistically significant, identifying increase of all baseline scores.

INTRODUCTION

Conventional magnetic resonance obtains anatomical information based on the water signal, spectroscopy allows us to obtain a metabolic spectrum of the brain based on the chemical composition of its metabolites reflected in a different resonance frequency known as "Chemical Shift", meaning that the evaluation of the brain spectrum is achieved based on the difference in the resonance frequency of its metabolites (Figure 1) (Michael, 2013; Andrea *et al*., 2014). There are several metabolites evaluated in magnetic resonance spectroscopy (Table 1), among them is the N-acetyl-aspartate (NAA), which is present in high concentrations in the brain, being greater in the gray substance than in the brain. in white matter, demonstrated by Koller *et al*. in 1984, who also established that (NAA) was present only in the central nervous system, mostly in neurons but not in glial cells, because of this it is used as a marker of neuronal viability. Anything that produces neuronal destruction, be it tumor, multiple sclerosis, Alzheimer's disease, among other causes, will cause a decrease

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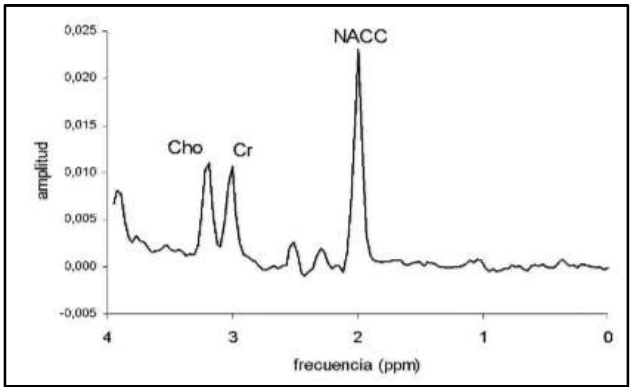


Figure 1. Distribution of metabolites evaluated in a normal cerebral magnetic resonance spectroscopy

Tab. 1. Metabolites detectable in the normal brain, along with its position in the spectrum

Metabolito	Abbreviation	Localization (pmm)
Lipids	Lip	0.9
Lactate	Lact	1,3
To the girl	Ala	1,47
Acetate	Ac	1,92
N-Acetyl-Aspartate	NAA	2,02
Glutamate	Glx	2,1
Glutamine	Glx	2,14
Succinate	Succ	2,42
Creatine	Creat	3,03
Hill	Cho	3,2
Scilloinositol	sI	3,35
Taurine	Tau	3,43
Myoinositol	Mi	3,55
Glycine	Gly	3,56
Creatine	Cr	3,93

in this metabolite, which will be reflected in the spectroscopy (Gülin *et al*., 2014; Saeed Fakhran, 2013). Traumatic brain injury (TBI) is defined as an assault to the brain caused by trauma of external origin that produces a compromise of the functional physical or psychosocial or cognitive abilities of the subject. In 2009, the CDC established that about (Andrea, 2014). 4 million attentions in the emergency department, hospitalization or death are related to head trauma, either alone or in combination with other injuries. Traffic accidents, falls, violence and sport accidents are the main causes of traumatic brain injury (Andrea, 2014; Gregory, 2015). It is the first cause of death or disability among the young population of the United States. The incidence rate is estimated at 100 per 100,000 people with 52,000 deaths per year.

The highest incidence is in people between 15 and 24 years old, and 75 years and older with a marked peak of incidence in children of 5 years or less (Octavian Adam, 2015). Its prevalence is estimated at 2.5 million to 6.5 million with the result of long-term functional commitments and permanent psychosocial or psychic and cognitive dysfunction of the subject. 4 million attendances in the emergency department, hospitalization or death are related to traumatic brain injury alone or in combination with other injuries (Michael, 2013; Grand Rounds, 2013). Traffic accidents, falls, violence and sports accidents are the main causes of traumatic brain injury. [2]From the point of view of the military population this definition includes additional specifications in relation to external forces, these may include, blow on the head by some object, the head hitting an object, antecedent of brain injury by the movement of acceleration / deceleration without any external trauma to the head, a foreign object penetrating the brain, or some force generated from an event such as an explosion (Andrea *et al*., 2014). In Mexico, within the Secretariat of the Armed Navy of Mexico, there is a specific registry of automobile accidents that occurred in orders of operations, where the military personnel who are performing their work, have come to suffer head injuries, from mild to severe, and even lethal; these unforeseen events have led to the need to keep the staff hospitalized, which after stabilization of the event in acute, it has been observed that some have sequelae in cognitive function, reason why they have had to keep out of the work activities, due to inability to develop them adequately. The determining factor in the condition of cognitive impairment is the early presence of behavioral and psychological symptoms, it has been determined that more than 90% of patients will present symptoms such as apathy, agitation, anxiety, depression, hallucinations, delusions throughout the disease. , aberrant motor activity, irritability, sleep and eating behavior disorders, euphoria or disinhibition (Gregory, 2015; Boleaga-Duran Bernardo, 2012). These factors are the determining factors in the significant decrease in the quality of life of patients and also of family members and caregivers. The lack of improvement in these symptoms, generates decrease in independence of the individual, which has been related to the increase in the consumption of psychotropic drugs, and in the number of premature hospitalization in an institution, since it increases the need for supervision and support in the personal care of the sufferer (Octavian Adam *et al*., 2015; Chi-Jen Chen, 2012).

Although naturally the tendency of traumatic brain injury is to the slow improvement of cognitive disorders, there is strong evidence regarding the effectiveness of the intervention of multidisciplinary and comprehensive rehabilitation teams compared with spontaneous recovery (Michael, 2014). The scientific basis of cognitive rehabilitation (CR) is located in some well-known biological phenomena. Neural plasticity has been known for more than two decades, and since then the capacity of the neuron to regenerate dendrites has been demonstrated. More recently, a group of researchers demonstrated the capacity for neuronal regeneration in cell cultures of subjects who died years ago due to non-neurological diseases, opening a giant question mark to the traditional conviction of the inability to regenerate the central nervous system.[21] The objective of rehabilitation is to improve the adaptive functioning of people within their families and in the places in which they live or work. The nature and severity of cognitive engagement varies widely. The attentional and memory deficits, the difficulties for new learning, and the alterations of the functions of goal setting, planning and monitoring of results, are among the most frequent and problematic (Kunling Xiong, 2014; Bogdanova and Verfaellie**,** 2012). Cognitive rehabilitation is based primarily on the guided practice of a set of tasks designed to stimulate or specifically train cognitive functions such as memory, attention or executive capabilities, which can be performed in a variety of formats and procedures (Kunling Xiong, 2014). It has been shown in clinical studies that in patients suffering from dementia and receiving cognitive rehabilitation, there is a significant reduction in the frequency and severity of behavioral and psychological symptoms, such as significant reduction of apathy and depression, anxiety and other behavioral symptoms (Laszlo *et al*., 2014; Chi-Jen Chen, 2012). However, none of the studies evaluated the relationship between clinical changes and changes in magnetic resonance spectroscopic imaging in this pathology.

Several studies of spectroscopy have revealed in Alzheimer's disease, considering creatine (Cr) as a stable internal reference, a decrease in N-acetyl-aspartate (NAA) and an increase in myo-Inositol (mI) compared to healthy subjects (Kunling Xiong, 2014; Laura Moretti, 2012), considering that alterations of choline (Co) have not been conclusive (Laura Moretti, 2012).

And in different studies in reference to Alzheimer's disease and other types of conditions that are categorized as neurodegenerative, such as dementias and even mild cognitive impairment, they have been characterized by a decrease in the metabolite N-Acetyl Aspartate, typically identified in the affected cerebral region, having mainly the prefrontal area, the caudate nucleus, and in some studies affection to the hippocampus. The N-acetyl Aspartate levels represent the severity of the disease and these levels are correlated with the results measured in neuropsychological tests (Stephen, 2009). It is also known that with mild cognitive impairment, the existing N-acetyl ratio will also be diminished. Aspartate / creatine, in addition to identifying the relationship that exists in the decrease of these metabolites and with cerebral atrophy and neuronal loss associated with carriers of mild cognitive impairment with family members suffering from Alzheimer's disease. Therefore, the established levels of these metabolites can be considered as indicators in the evaluation of the progression of the disease. In addition, due to the results (Bartha R. 2008) of the increase of N-Acetyl Aspartate at the hippocampus level in the spectroscopy after the treatment with Donezepilo, it is considered that the levels of N-Acetyl Aspartate reflects the recovery and functional integrity of the Central Nervous System (Stephen, 2009; Laszlo *et al*., 2014; Laura Moretti, 2012).

MATERIAL AND METHODS

This work is a quasi-experimental analytical study, with a pre-post intervention design or determined as a trial of the usual clinical practice, was carried out at the Naval General Hospital of High Specialty, located in Mexico City, DF, during the month of January 2016 to October 2017.

Target population

During the search for a base parameter to determine the population sample to study, no similar or similar study was found. Therefore, the article "the effect of behavioral therapy on N-Acetyl-Aspartate acid at the level of quark in adults with obsessive-compulsive disorder" is taken from Stephen P.H. Whiteside, April 2011, published in the journal Psychiatry Research: Neuroimaging. Taking into account this study and taking into account the calculation formula of comparison of two paired means. It was calculated with the statistical program Stata version 12.0. Calculating a minimum required sample of 20 patients.

$$n = \frac{2(Z_\alpha + Z_\beta)^2 * S^2}{d^2}$$

Zα = Value of Z corresponding to the desired risk (two tails)

Zβ = Value of Z corresponding to the desired risk (to 80%)

S2 = Variance of the control group to be detected (article)

d2 = Minimum value of the difference you want to be detected

Readable population

The universe of study includes the personnel belonging to the Secretary of the Armed Navy of Mexico, who are currently in active service, of which they have a history of head trauma.The stipulated sample of the patients included in the study was taken from those previously mentioned, who were included in cognitive rehabilitation by the psychiatry and psychology services due to the diagnosis of cognitive impairment diagnosed with the mini cognitive test, evaluating them with spectroscopy by magnetic resonance prior to rehabilitation and at the end of it.

Selection criteria

The inclusion of military servicemen in the active service, military with a history of closed head injury, cognitive impairment diagnosed with the mini-cognitive test, those who are in treatment with Psychiatry and Psychology, and those who still do not receive it, were taken into account as inclusion criteria. treatment with cognitive rehabilitation. Likewise, exclusion criteria were considered for patients with a diagnosis or history of cerebral infarction or hemorrhage, subdural hematoma, sensory loss, confutional syndrome, brain tumor, history of intoxication, hydrocephalus, chronic degenerative conditions that can cause deterioration. mild cognitive by itself. And the criteria for elimination were those subjects who during the process did not satisfactorily complete the treatment, those who did not comply with the studies carried out, subjects who wish to stop participating in the study during the intervention, those who died during the evaluation period.

Statistical analysis and interpretation of data

We analyzed 20 male patients with an average age and standard deviation of 30.9 +/- 5.8 (range 23-43) years. In 7 cases (35.0%) the TBI was mild and in 13 (65.0%) moderate. The months elapsed between the TBI and the medical treatment were on average 4.7 +/- 4.1 (range 1-16) months and between TBI and CR of 6.9 +/- 5.5 (range 2-24) months. In the basal state (pre-treatment) there was no difference between the average ages according to the TBI grade with 30.0 +/- 3.9 years for the mild ones versus 31.4 +/- 6.7 years for the moderate ones (p = 0.60 according to Student's t); however, age correlated significantly with the variables in Table 2. It was suggested that the older the time between TBI and medical treatment and CR; On the other hand, the younger the values of cognitive evaluations were.

Table 2. Correlation of age with cognitive variables in the baseline (pre-treatment) of patients with TBI

CORRELATED VARIABLE	COEFICIENTE*	P
Time between TBI and medical treatment.	0.599	0.005
Time between TBI and RC	0.654	0.002
MMC1	-0.640	0.002
Front NNA 1	-0.862	0.0001
NNA Cr frontal 1	-0.824	0.0001
NNA hippocampus 1	-0.686	0.001
NNA Cr hippocampus	-0.689	0.001

* The correlation coefficient R of Pearson was applied.

Changes in cognitive variables on a qualitative scale were not statistically significant, however in the immediate recall of 11 patients (55%) that before treatment was affected, the proportion was reduced to 30%, however p = 0.06 (see Table 3).

However, in the quantitative variables (all had a normal distribution according to the Shapiro-Wilk statistic), the pre vs. post differences were statistically significant, as shown in Table 4; note that all baseline scores increased. To observe the effect of age on the changes of the qualitative variables, the age averages were compared, having classified the changes in three pre-post levels as: Affected-affected; Affected-normal and Normal-normal.

Only in two variables (immediate recall and deferred recall) the averages of age were significantly different between the levels of change. As can be seen in table 5, patients who had immediate or delayed recall at the baseline or pre-treatment status but who were normal after treatment were significantly younger (26.2 years for immediate recall and 25.7 years). For deferred recollection) that those that did not change

Table 3. Change in the proportions of cognitive variables before vs post-treatment of cognitive rehabilitation (% of affected cases)

VARIABLE	MEASUREMENT			P*
	PRE	POST	DIFFERENCE (%)	
O. Temporal	7 (35%)	3 (15%)	20	0.12
O. Space	3 (15%)	1 (5%)	10	0.50
R. Immediate	11 (55%)	6 (30%)	25	0.06
A-calculation	15 (75%)	11 (55%)	20	0.12
R. Deferred	16 (80%)	12 (60%)	20	0.12
Language	3 (15%)	1 (5%)	10	0.50
EEG	7 (35%)	5 (25%)	10	0.50

* The McNemar test was applied for related samples

Table 4. Comparison of averages before vs post treatment in patients with traumatic brain injury

		HALF	N	STANDARD DEVIATION	P*
Pair 1	SCORE MMC 1	27.35	20	1.461	0.0001
	SCORE MMC 2	30.90	20	2.573	
Pair 2	NAA1Fron	1.470500	20	.4059359	0.0001
	NAA2front	1.738500	20	.3962226	
Pair 3	NAA/Cr1Fron	1.221500	20	.3381416	0.0001
	NAA/Cr2	1.4460	20	.32997	
Pair 4	NAA1Hipo	1.657500	20	.4382246	0.004
	NAA2hipo	1.821500	20	.5168760	
Pair 5	NAA/Cr1Hipo	1.269500	20	.3365221	0.004
	NAA/Cr2hipo	1.395000	20	.3982263	

* Student t was applied for related samples

Table 5. Comparison of the averages of age according to levels of change after treatment in the variables immediate recall and delayed recall of patients with TBI

Levels of pre-post-treatment change	case numbers	Immediate memory	case numbers	Deferred memory
Affected-affected	6	33.1 +/- 6.1	12	32.3 +/- 6.5
Affected-normal	5	26.2 +/- 2.5	4	25.7 +/- 0.9
Normal-normal	9	32.1 +/- 5.8	4	32.0 +/- 3.6
p*		0.05		0.03

*The Kruskal-Wallis Ranks Test was applied.

Coefficients (a)

Model		Non-standardized coefficients		Standardized coefficients	T	Sig.
		B	Standard error	Beta		
1						
	(Constant)	9.647	1.794		5.378	.000
AGE	-.197	.057	-.632	-3.456	.003	

a Dependent variable: CHANGE MMC

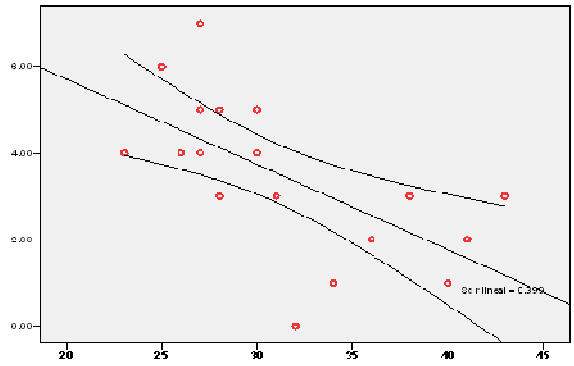
So, pre-post change score of MMC = 9.647 - 0.197 (age)

Table 6. Comparison of averages of the pre-post change score in patients with TBI.

	AGE	N	HALF	STANDARD DEVIATION	P*
CHANGE NNA FRONTAL	31-43	8	.2650	.18040	0.95
	23-30	12	.2700	.17571	
CHANGE NNA/CR FRONTAL	31-43	8	.2213	.14904	0.93
	23-30	12	.2267	.14877	
CHANGE NNA HIPOCAMPO	31-43	8	.0625	.12303	0.06
	23-30	12	.2317	.25544	
CHANGE NNA/CR HIPOCAMPO	31-43	8	.0475	.09573	0.06
	23-30	12	.1775	.19596	
CHANGE MMC	31-43	8	1.8750	1.12599	0.0001
	23-30	12	4.6667	1.23091	

*Student t was applied for independent samples.

(of affected affected continued or normal continued normal) whose average ages were greater than 30 years. Now, with respect to quantitative variables, the score was changed from pre to post and first these changes were correlated with age and in which case it was observed that the younger the score was, the favorable change in the MMC variable with a coefficient of correlation R-0.632 (p = 0.003), see graph 1:



Graph 1. Correlation of age with the change of pre-post-treatment scores of the variable MMC in patients with TBI

Table 7. Comparison of averages of change in hippocampal NNA variables in patients treated according to the degree of TBI

Variable	Degree of TBI		P*
	MILD	MODERATE	
Change hippocampus NNA	0.03 +/- 0.1	0.23 +/- 0.2	0.02
Change hippocampus NNA/CR	0.02 +/- 0.09	0.17 +/- 0.1	0.02

* Student t was applied for independent samples.

It is evident that in the older patients the change in the MMC score was much lower than in the younger age. In fact, the prediction of the amount of the change will be: Another way of observing the relationship between age and the change scores of the quantitative variables and since the overall mean age was 30.9 years, if it is divided into two age subgroups: one of 31-43 years and another from 23-30 the results are those that are recorded in table 6.Obviously, only the change in MMC was significant when comparing the means of change between those in the group of 31-43 years versus those of 23-30 years. In this case it is shown that those aged 31-43 years only manage to change 1.87 points on average, while those of 23-30 years reach up to 4.66 points of change in MMC (p = 0.0001). Finally, the degree of TBI only influenced the changes of NCA hippocampus and NNA Cr hippocampus. Table 7 shows that patients with mild TBI changed very little in both variables 0.03 points and 0.02 points respectively and, in contrast, those of moderate TBI changed to 0.23 and 0.17 points and in both variables the differences are significant between the two TBI grade in favor of greater change in those of moderate TBI.

DISCUSSION

Laszlo L. Mechtle and collaborators identified in 2014 that the relationship between N-acetyl Aspartate and creatine is diminished in mild cognitive impairment, and that Kunling Xiong identified the relationship that exists in the decrease of these metabolites with brain atrophy. and neuronal loss associated with carriers of mild cognitive impairment with family members suffering from Alzheimer's disease. The levels of N-acetyl Aspartate represent the severity of the disease and these levels are correlated with the results measured in neuropsychological tests according to the research of Joshua D. Halbauer, J. Wesson Ashford. Therefore, the established levels of these metabolites can be considered as indicators in the evaluation of the progression of the disease. In the present research work, it was identified that baseline baseline studies of patients with cognitive impairment diagnosed by means of the applied mini cognitive mental examination are mostly related to a decrease in N-Acetyl-Aspartate. It has been shown in clinical studies that in patients suffering from dementia and receiving cognitive rehabilitation, there is a significant reduction in the frequency and severity of behavioral and psychological symptoms, such as significant reduction of apathy and depression, anxiety and other behavioral symptoms. However, none of the studies has assessed the relationship between clinical changes and changes in spectroscopic magnetic resonance imaging in this pathology. This study demonstrates an objective way by image the clinical improvement of the patient with cognitive deterioration, by means of the measurement of N-acetyl-aspartate with an increase of its levels after treatment compared with its basal levels, thus identifying that there is a change of pre after rehabilitation, and first correlated these changes with age and in which case it was observed that the younger the age the favorable change score was in the variable MMC with a correlation coefficient r - 0.632 (p = 0.003), the change in MMC it was significant when comparing the means of change between those in the group of 31-43 years versus those in 23-30 years. In this case it is shown that those aged 31-43 years only manage to change 1.87 points on average, while those of 23-30 years reach up to 4.66 points of change in MMC (p = 0.0001).

Conclusion

Traumatic brain injury causes a decrease in the functional, physical, psychosocial and / or cognitive abilities of some subject, and the nature and severity of the cognitive commitment varies widely. The attentional and memory deficits, the difficulties for new learning, and the alterations of the functions of goal setting, planning and monitoring of results, are among the most frequent and problematic. Conditioning problems in the lifestyle of those who suffer from it and their caregivers. Cognitive rehabilitation aims to improve the adaptive functioning of people in their families and in the places where they live or work. With the present work, it is concluded that there are significant results through the measurement of the metabolite N-Acetyl-Aspartate in patients under 31 years of age, but not in older patients, finding a correlation in the improvement of cognitive deterioration with the initiation of early therapy with rehabilitation not statistically significant, but observing a significant percentage of patients evaluated. Patients with moderate head trauma had better results in the clinical evaluation with the cognitive mini mental examination and in N-Acetyl-Aspartate metabolite levels, patients with mild head trauma changed very little in both variables 0.03 points and 0.02 points respectively and, in contrast, those of moderate TBI changed to 0.23 and 0.17 points and in both variables the differences are significant between the two degrees of TBI in favor of greater change in those of moderate TBI

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