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Disorder verbal memory in alcoholics after delirium tremens

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Abstract. – AIMS, Alcohol delirium tremens suggests dysfunction of numerous brain regions. Several Authors suggest that alcohol and withdrawal from alcohol could cause neurotoxic lesions in the frontal lobe and thereby affect cognitive function. However, it is not that well known whether the consequences of the damage following delirium are only quantitative or qualitative.

PATIENTS AND METHODS, Thirty alcohol-dependent patients after alcohol delirium (ADT-n1 = 30), and 30 alcohol-dependent patients without alcohol delirium (ALC-n2=30) were compared with neuropsychological test-battery. [(Wechsler Bellevue Intelligence Scale – WB form I, Wechsler memory scale and Rey Auditory Verbal Learning Test (RAVLT)]. Examinees were selected as equivalent pairs, in such a manner that they were of approximately same age, i.e. age difference was 0-5 years, they were of the same education level, and difference in the duration of drinking was not more than 3 years.

RESULTS, In the group of ADT patients, IQ was 97.53, while it is 109.53 for ALC patients. Mental deterioration of the examined group is 40, and in the control group 13. Group of ADT patients had significantly lower achievements on subtests: arithmetic, block design and digit symbol. ADT patients' average memory quotient (MQ) is 81.8, which is three standard deviations lower compared to ALC patients (MQ 102.2) and standard values, according to Wechsler. In the first repetition of the series of 15 words RAVLT, is no difference (t-test=1.88; $p > 0.05$), while the difference in other repetitions is significant. Difference is also statistically significant regarding recollection after 30 minutes (t-test=3.66; $p < 0.05$).

CONCLUSION, There is qualitative difference in cognitive deficiencies in alcoholics with delirium tremens and those with no alcohol delirium, while the predominant pathology of the cognitive-amnestic deficiency is in compliance with the dysfunction of the prefrontal lobe. Following alcohol delirium, verbal memory disorders occur within the intellectual decrease and attention disorder in general.

Key Words:
Disorder, Verbal memory, Alcoholism, Delirium tremens.

Introduction

It has been asserted that persons who drink for extended periods of time have poorer results on tests of specific neuropsychological performances, although they show no apparent signs of brain damage[1-7]. Researchers were examining impact of the abstinence, duration of drinking and gender on cognitive damages, but results were inconsistent[8-10]. Desire to determine integral instrument which would bring consistent results for cognitive damages caused by alcohol has so far remained with no success. Reason for this failure lies in numerous factors influencing the development of alcohol dependency, such as heredity, age of the onset of drinking, duration of drinking, type of alcohol drink and so on. Distinct problem are consequences of the alcohol disease, where the abstinence crisis stands out as significant agent. Multiple abstinence crises increase vulnerability for brain dysfunctions[11]. One of the mechanisms leading to this type of brain damages is amplification of the excitotoxicity, which develops as a consequence of the increase of excitatory neurotransmitters[12]. Furthermore, abstinence crisis causes changes in certain neuroendocrine systems which augment psychopathology developed due to the alcohol intake. Hormonal system playing significant role is hypothalamic-pituitary-adrenal (HPA) axis. Abstinence syndrome activates HPA axis, which leads to the increased secretion of corticoids[13]. Glicocorticoids, type of corticoids, influence neural excitability of the CNS. Extended stimulation of these neurons causes brain damages, especially in hippocampus[14]. Progressive increase of neurochemical and neuroendocrine alterations occurring during abstinence crises comprise biological foundation of cognitive deficits related to alcohol intake[15]. The most severe form of abstinence crisis is alcohol withdrawal delirium. Consideration whether alcohol

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withdrawal delirium is merely a manifestation of the severe form of abstinence crisis or it is a syndrome developing on the foundation of previously altered brain structure and function is, from the clinical point of view, very interesting. In order to make this distinction, researches have been done, attempting to detect cognitive deficits in persons who had delirium and those who had only the diagnosis of alcohol dependency. One research has shown that there is no significant difference in cognitive functioning between alcohol dependent persons who had no abstinence crises, those with mild and moderately severe crises, while alcohol dependent patients following delirium shown significantly lower results, particularly in the area of recognition[16]. Another research confirms decline of cognitive functioning following delirium tremens and determines that the degree of the damage correlates with the psychomotor agitation and intensity of hallucinations[17]. Further researches have confirmed that cognitive sequels after the delirium are long lasting[18]. The aim of this paper was to establish the difference in the verbal memory disorder between alcohol dependent patients who had delirium tremens and those who did not, based on neuropsychological examination.

Patients and Methods

Research is prospective clinical study. It has been conducted at the Clinic for Substance related disorders of the Clinical of Psychiatry in the Clinical Centre Vojvodina in Novi Sad, Serbia.

In forming of the sample for the research, group of 30 alcohol dependent patients (n_1=30) following delirium tremens was taken. Requirements for the diagnosis are the criteria of the F10.40 code (Delirium tremens), tenth international classification of mental and behavioural disorders (ICD-10)[19]. *Excluding criteria* are previously diagnosed delirious states, suffered craniocerebral trauma, presence of diagnosed endocranial tumours, diagnosed temporal epilepsy, presence of psychotic disorders, current presence of affective disorders, mental deficiency syndrome, diagnosis of other substance related disorders, existence of neurological and neuromuscular damages.

Exploration of patients was conducted three months after delirium tremens, since it is believed that is the period in which the abstinence symptoms of transient brain syndrome are persisting.

Control group was comprised of 30 alcohol dependent patients (n_2=30) who did not have delirium tremens. All of them met criteria for the F10.2 code (Alcohol dependence) ICD-10. Excluding criteria were the same.

Testing has also been conducted three months following the establishing of abstinence. Patients in this group have been chosen as equivalents to the patients of the experimental group, i.e.:

1. They were of approximately same age, i.e. age difference ranged 0-5 years.
2. They were of the same education level.
3. Difference in duration of drinking was not more than 3 years.

Following instruments were used for collecting data:

A simple *form*, specially developed for the needs of this research, included the following items: age, education level, and duration of drinking, duration of abstinence, number of abstinences, heredity, alcohol liver lesions and symptomatic epileptic seizures caused by alcohol.

Neuropsychological Tests

Wechsler Bellevue Intelligence Scale (WB form I)[20]

This test is comprised of five verbal and five non-verbal subtests. Intelligence quotient (IQ) consists of verbal intelligence quotient (IQv) and performance intelligence quotient (IQp). In 1986, Wechsler made a revision of the described scale, and today mainly revised version of Wechsler intelligence scale is used. Since the battery of tests used in this research is large, we have decided to use the original Wechsler intelligence scale. We find justification for such a decision in the work of Oscar-Berman et al[21]. Testing alcohol dependent patients, he found out that the tests used to identify amnestic syndrome, in other words difference between the intelligence quotient and results of memory tests, were efficient in both combinations (WMS or WMS-R). Reliability: Reliability coefficients for the subtests range from 0.62 to 0.88. The Verbal IQ, Performance IQ, and Full Scale IQ have reliability coefficients of 0.84, 0.86, and 0.90, respectively[22]. Validity: The Authors investigate correlations between the WBIS and other tests of cognitive ability. The coefficients are e as follows: Stanford-Binet, 1937 rev., 062; Otis, 0.73; Raven Progressive Matrices, 0.55, and the Army Alpha test, 0.53.

Wechsler Memory Scale (WMS)[23]

Includes mainly the domain of verbal memory, and only in one subtest of non-verbal memory. Importance of this scale is that we can compare results of the "memory" (expressed as memory quotient) with the intelligence quotient from the Wechsler intelligence scale. This scale is used for determining the interrelation between the memory and general mental abilities. Reliability: The reliability coefficients for the WMS-III Primary subtests and Primary Indexes were on average found to be higher than for the WMS-R. Internal consistency reliability coefficients ranged for .70s to the .90s. Validity: Correlation with the WMS-R was not direct because of the many changes in the scales. The Verbal Memory of the WMS-R had a .72 correlation coefficient with the Auditory Immediate, .68 with the Auditory Delayed, and .65 with General Memory of the WMS-III. The General Memory of the WMS-R and the Auditory Immediate .73, Auditory Delay .69, and general memory .67 of the WMS-III. As expected the correlations were lower for visually presented material with .34 for verbal memory and visual memory indexes. When correlated with the Children's Memory Scale, the WMS-III auditory indexes correlated highest with the corresponding CMS indexes. Studies comparing the WMS-III and the WIAT show highest correlations between the WMS-III auditory indexes and working memory indexes and the WIAT subtests and composites, similar to results found with the CMS and the WIAT. In comparing the WMS-III with the WAIS-III there is a pattern of the auditory memory correlating more strongly with the VIQ and the visual memory measures correlating more strongly with the PIQ as an indication of convergent and divergent validity; while they are related, they measure different constructs.

Rey Auditory Verbal Learning Test (RAVLT)

Originally developed in the 1940s, the RAVLT[24] has evolved over the years, and several variations of the test have emerged. The standard RAVLT format starts with a list of 15 words, which an examiner reads aloud at the rate of one per second. The patient's task is to repeat all the words he or she can remember, in any order. This procedure is carried out a total of five times. Then the examiner presents a second list of 15 words, allowing the patient only one attempt at recall. Immediately following this, the patient is asked to remember as many words as possible from the first list. The RAVLT has proven useful in evaluating verbal learning and memory, including proactive inhibition, retroactive inhibition, retention, encoding versus retrieval, and subjective organization. Reported reliability for the Rey Auditory Verbal Learning Test was varied; 0.70 for List A and 0.38 for recall of List B. Test-retest reliability for a one-year interval between test administration was reported moderate, 0.55[25]. The RAVT is closely correlated with the California Test of Verbal Learning-Children Version. Correlation ratings of 0.50 to 0.65 with other factor grouping and other learning tools[26] supports RAVLT validity. Such functions as acquisition, storage, and retrieval were indicated as measures for the test by factor analytic studies.

We compared our groups on following items: age, education level, and duration of drinking, duration of abstinence, number of abstinences, heredity, alcohol liver lesions and symptomatic epileptic seizures caused by alcohol.

Statistical Analysis

Within the statistical data we used non parametric analysis (chi Square); significance of differences between dependent variables' means was tested by *t*-test. Obtained data have been processes in appropriate PC statistical program (Statistic for Windows version 7.0), while the graphic displays were made in Microsoft Office Excel 2007.

Results

Data from the form (Table I)

Sample included examinees from the age of 30-60 years. Average age of the examined group was 46.9 (M1=53; SD1=4.32), and in the control group 46, 7 (M2=53; SD2=3.93). There is no statistically significant difference regarding the age (χ^2 =1.38; DF=5; $p > 0.05$).

The examined and control group were, as regards education level, fully equalised: in each group, 4 examinees had primary education, 17 finished high school and 9 examinees finished higher school and university.

Average duration of drinking of alcohol dependent patients who had delirium tremens was 18.6 years, and in control group 16.4 years. Statistical analysis (*t*-test=0.876; $p > 0.05$) showed no statistically significant difference.

Based on the given data, equalising of the groups, according to the three given criteria, was confirmed.

Table I. Data from the form.

	ADT	Alc	Statistic test	*p*
Age	46.9 M1-53 SD1-4.32	46.7 M2-52 SD2-3.93	$\chi^2 = 1.38$	> 0.05
Education level				
Primary	4	4	0	1
High school	17	17		
Higher/university	9	9		
Duration of drinking (years)	18.6	16.4	*t*-test = 0.876	> 0.05
Without abstinence > 3 months	8	12	$\chi^2 = 1.2$	> 0.05
No of abstinences > 3 months	1.6	1.33	*t*-test = 2.71	= 0.54
Average duration of abstinence	9.3	7.7	*t*-test = 1.61	= 0.11
Positive family heredity	16	18	$\chi^2 = 2.15$	= 0.34
Alcohol liver lesion	12	14	$\chi^2 = 0.67$	= 0.79
Epileptic symptoms	18	20	$\chi^2 = 0.28$	= 0.78

In our material, 8 alcohol dependent patients from the first and 12 from the second group have never established abstinence longer than three months. Statistical analysis revealed no statistically significant difference ($\chi^2 = 1.2$; DF = 2; $p > 0.05$). Delirious patients had established, in average, 1, 6 abstinences, and non-delirious 1.33. Average duration of abstinence in patients with delirium was 9, 3 months, and in non-delirious 7.7. Difference was not statistically significant (*t*-test = 1.61; $p = 0.11$).

In families of both groups of alcohol dependent patients, alcoholism was present in 16 cases, while in 2 cases other mental disorders existed in the control group. Difference between groups was not statistically significant ($\chi^2 = 2.15$; DF = 2; $p = 0.34$).

Diagnosis of alcohol liver lesion, established based on lab results, was confirmed in 12 patients with delirium and 14 patients with no delirium. Difference was not statistically significant ($\chi^2 = 0.67$; $p = 0.79$). Symptomatic epileptic seizures caused by alcohol appeared in 18 patients with delirium and 20 with no delirium. Difference was not statistically significant ($\chi^2 = 0.28$; $p = 0.78$).

Results of the Neuropsychological Assessment of Memory Functions

Results of Wechsler Bellevue Intelligence Scale (Table II)

IQ for the group of alcohol dependent patients with delirium is 97.53, and for those with no delirium 109, 53. Mental deterioration of the examined group is 40, while in control group it is 13.

Group of alcohol dependent patients who had alcohol delirium had significantly poorer achievements (more than 4 pondered scores) on arithmetic, block design and digit symbol.

Wechsler Memory Scale (WMS)

Alcohol dependent patients, following delirium, have poorer results than alcohol dependent patients with no delirium on subtests of mental control and associative learning, and compared to standard values on subtest of logical memory too (Table III).

Results of Rey Auditory Verbal Learning Test (RAVLT)

Rey Auditory Verbal Learning Test (Table IV) Learning curve of RAVLT (Figure 1)

Compared to the standard values according to Rey, expected values are decreased in both groups. The difference between the examined and control group is not statistically significant only in the first repetition of the word series of 15 words (*t*-test = 1.88; $p > 0.05$), while it is significant in other repetitions. Learning curve for alcohol dependent patients with delirium has slower progression and "more flattened learning plateau", approximating it by that to patients with frontal lobe syndrome. Difference is also statistically significant regarding recollection after 30 minutes (*t*-test=3.66; $p < 0.05$).

Table II. Wechsler bellevue intelligence scale.

Subtest	ADT*	Alc**	Difference	Significant difference***
Information	11.3	12.2	0.9	
Comprehension	9.5	12.9	3.4	
Arithmetic	5.7	9.8	4.1	*
Similarities	10.8	12	1.2	
Digit span	5.7	7.3	1.8	
Picture completion	9.8	10.2	0.4	
Picture arrangement	7.3	8.7	1.4	
Block design	6.8	11.6	4.8	*
Object assembly	5.4	8.3	2.9	
Digit symbol	3.7	8.1	4.4	*
IQ	97.53	109.57		

*ADT alcohol dependent patients with delirium tremens; **Alc alcohol dependent patients with no delirium tremens; ***Difference on subtests is significant if exceeding 4 pondered scores. IQ: Intelligence quotient.

Discussion

Cognitive deficits related to the abnormal functioning of the prefrontal cortex are recognized in alcoholism, independently from co-morbid conditions [27]. In this paper, 30 alcohol dependent patients who had delirium tremens and 30 patients with no delirium tremens were treated. Standardized alcohology questionnaire shown no statistically significant difference in demographic and alcohologic characteristics. Levelling groups, we excluded influence of the age, duration of drinking and primary intellectual level on the consequences of alcohol and alcohol delirium. Obtained data, therefore, have no epidemiological significance.

Average age of delirious patients in our research is 46.67 years. Doniger[28] asserts that the risk increases after the age of 65. One of the main indicators of the dependency syndrome is appearance of the abstinence symptoms following the cessation in drinking. Most often, nervous system diseases are complications of alcoholism. Alcohol epilepsies occur in 10-15% of hospitalized alcohol dependent patients[29]. Alcohol epileptic seizures most often accompany alcohol delirium. In our research, we found no statistically significant difference between persons with epileptic seizures who had delirium and those who did not. Liver damages occurred in 40% in alcohol dependent patients following delirium, 46% in alcohol dependent patients with no delirium, which is not statistically significant and implies that alcohol delirium cannot be brought into immediate connection with hepatic dysfunctions.

In 1945, Wechsler[23] standardized his Intelligence Scale for the first time (Wechsler-Bellavue

Table III. Wechsler memory scale.

Subtest	ADT	Alc	Standards by wechsler		ADT/ standard	Alc/ standard	ADT/ Alc
			Me*	SD**			
Information	5.8	5.9	5.7	0.4	0	0	0
Orientation	6.0	6.0	6.0	0	0	0	0
Mental control	2.8	5.3	6.6	1.9	-2SD	0	-1.5SD
Logical memory	4.6	6.7	8.0	2.5	-1SD	0	0
Digit span	8.7	10.7	10.2	2.2	0	0	0
Visual reproduction	5.3	10.4	8.35	3.1	0	0	0
Associative learning	9.8	13.7	13.9	3.1	-1SD	0	-1SD
MQ	81.8	102.2	102	6.5	-3SD	0	-3SD

Me: Median; SD: Standard deviation; MQ: Memory quotient.

Table IV. Rey auditory verbal learning test (RAVLT).

Repetition	ADT	Alc	Stan.*	ADT/ Alc T test	ADT/ Stan. T test	Alc/ Stan. T test	p ADT/ Alc	p ADT/ Stan.	p Alc/ Stan.
1	4.6	5.3	8.6	1.88	2.1	3.5	> 0.05	< 0.01	< 0.01
2	5.7	8.0	11.6	4.46	4.2	3.0	< 0.01	< 0.01	< 0.01
3	5.8	8.9	13.4	5.14	5.3	3.2	< 0.01	< 0.01	< 0.01
4	7.1	9.9	13.8	4.04	4.6	4.6	< 0.01	< 0.01	< 0.01
5	7.2	10.4	14	4.04	4.9	4.3	< 0.01	< 0.01	< 0.01
Recollection	6.4	9.9	–	3.36	–	–	< 0.01	–	–

Stan.: Standard values by rey.

form I) on 1080 examinees. He did not aim to determine the essence of the intelligence at that time, but to develop a good instrument for measuring effects of the intelligence. Even nowadays the measure of "general intelligence" presents useful operational concept which shows the level of intellectual functioning of examinees. Intelligence quotient (IQ) is comprised of verbal intelligence quotient (IQv) and performance intelligence quotient (IQp). Such a division of intelligence on verbal and performance part finds no full justification in neuropsychology, since these functions often overlap within one scale. At the same time, subtests don't assess clear neuropsychological functions, hence engaging more brain systems within each subtest. Due to all previously said, interrelation of achievements on particular subtests is used as the basic assessment material.

For the group of alcohol dependent patients with delirium, IQ is 97.53, while for the alcohol dependent patients with no delirium it is 109.53. Mental deterioration of the examined group is 40, which is an indicator of highly likely deterioration, while in the control group it is 13, which classifies them into category of potential deterioration. Given data indicate more significant intellectual decline of organic brain syndrome type in the group of alcohol dependent patients who had alcohol delirium.

Alcohol dependent patients who had alcohol delirium also have poorer achievements on digit symbol, picture arrangement, digit span and arithmetic. These three subtests and digit span subtest fall into the group of instable tests. Lower achievements on these subtests indicate cognitive impairment within mental deterioration.

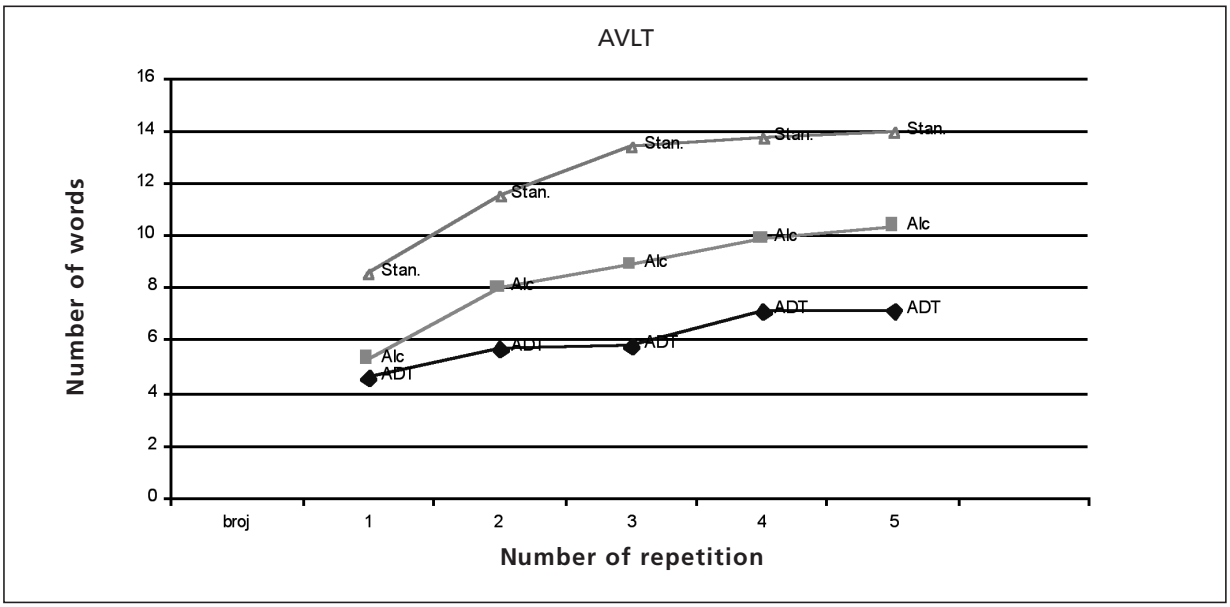

Figure 1. Learning curve of RAVLT,

Apart from the reduced attention, group of alcohol dependent patients with no delirium has reduces sequential thinking and social functioning (low "picture arrangement" scores). Damage to the amygdale and right prefrontal cortex are important in the processing of social information and in the recognition and attribution of complex mental states. Our data suggest that the functional capacity of this social cognitive brain network is not spared in patients with alcoholism. Other Authors obtained similar results, as well[30].

Compared to the control group, the examined group has poorer achievements on instable subtests, which is one of the signs of organic brain decline. This has also been confirmed by the higher deterioration index in the group of "delirious alcohol dependent patients".

Difference in digit span is not significant, since the score is low in both groups. Based on the results of factorial analysis, Kaufman[1] deduces that arithmetic, digit span and digit symbol are the most sensitive subtests on the factor of attention distractibility. It can be deduced from this that there is pronounced factor of distractibility in both groups, i.e. that the attention is decreased. Low scores on "object assembly" indicate poorer visual-motor coordination in productive form. Both of these functions, attention and productive form of visual-motor coordination, are mainly related to the prefrontal lobe. In his research, Loeber et al[31] followed changes in cognitive functioning of patients addicted to alcohol who had multiple withdrawal crises and those who are not addicted to alcohol. He tested them following the detoxification, after three months and after six months. Examinees had significantly poorer results than the control group, on first and second measurement, especially on subtests of attention and executive functions. This study gives evidence that repeated alcohol withdrawal crises can be related to decreased brain plasticity.

Wechsler's memory scale mainly covers area of verbal memory, and only on one subtest nonverbal memory. Importance of this scale is that the results of "remembering" (expressed as memory quotient) can be compared to the quotient of the Wechsler scale of intelligence. This is of high importance for it indicates mutual relation of memory and general mental abilities. Intelligence quotient in the group of alcohol dependent patients who had alcohol delirium is 97.5, and memory quotient 81.8, making the difference in quotients 15.7. Difference between intelligence quotient (IQ=109.5) and memory quotient (MQ=102.2) in alcohol dependent patients with no delirium is significantly lower, and amounts to 7.3. Result points to more isolated memory disorder in patients with delirium. This is also confirmed by the data that the MQ is 3 standard deviations lower compared to the standard, expected values in the group of alcohol dependent patients with delirium.

Following alcohol delirium, alcohol dependent patients have lower scores on subtests: mental control, logical memory and associative learning, compared to standard values. These subtests belong to verbal tests, in other words, scales of verbal memory. Mental control subtest points to the function of attention and concentration. Lack of flexibility, i.e. rigidity in thinking, is manifested in inability to change mental sets, something that poor results of "associative learning" points to. Poorer achievements on subtest logical memory are indicators of "frontal type" memory disorder. Low achievements mental control, logical memory and associative learning subtests suggest dysfunction of the prefrontal lobe.

Compared to standard values, alcohol dependent patients have no isolated poorer achievements on the memory scale. It has also been confirmed in one similar research[32] that there is no difference in logical memory and visual retention between alcohol dependent persons and those who are not. Man et al[33] got similar results that alcohol dependent persons have no poorer results on Benton visual retention test and logical memory test.

While logical memory and visual retention do not differ between persons addicted to alcohol and those who are not, addicted ones have shown apparent and persistent decline in examinations which include memory of verbal materials, procedure similar to Rey AVLT. That supports the research suggesting that AVLT can be more sensitive to detecting memory disorders in clinical population, since it is less prone to compensatory strategies helping learning[34].

Results we obtained in our research are similar. Expected values, compared to standard values by Rey, are decreased in both groups. Difference between the examined and control group is not statistically significant in the first repetition of the series of 15 words, while it is significant in other repetitions. Curve of learning in alcoholics with delirium has slower progression and "more flattened learning plateau", which approximates it to patients with frontal lobe syndrome. Difference is also statistically significant regarding recollection.

Conclusions

Alcohol dependent patients who had alcohol delirium have poorer level of intellectual functioning than alcohol dependent patients who had no delirium, and are of approximately same age, duration of drinking and education level. Such intellectual decline is sequel of mental deterioration, which is most prominently observed in deficiency of attention and productive form of visual-motor coordination which are, mainly, related to the prefrontal lobe. Isolated memory disorder follows alcohol delirium, while it has not been registered in alcohol dependent persons. Memory deficiencies are manifested through low achievements on subtests of mental control, logical memory and associative learning, which also indicate dysfunction of prefrontal lobe.

Auditory verbal learning is decreased in both groups. Curve of auditory learning in alcoholics with delirium has slower progression and "more flattened learning plateau", which approximates it to patients with frontal lobe syndrome. Following alcohol delirium, verbal memory disorders occur within the global intellectual decrease and attention disorder in general.

Based on everything previously said, it can be assumed that there is qualitative difference in cognitive deficiencies in alcohol dependent patients who had delirium and those with no alcohol delirium, while the predominant pathology of the cognitive-amnestic deficiency following delirium is in compliance with the dysfunction of the prefrontal lobe.

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