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Assessment of regional cerebral blood flow in patients with early and late onset alcohol dependence: SPECT study

Erken ve geç başlangıçlı alkol bağımlılarında bölgesel beyin kan akımının değerlendirilmesi: SPECT çalışması

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Abstract

Aim: Alcohol dependence has negative effects on the structure and functionality of the brain. The age of onset of alcohol is an important parameter in the grouping of alcoholics. The aim of this study is to compare whether regional cerebral blood flow (r-CBF) values differ between early (EO) versus late onset (LO) alcoholic patients.

Methods: A total of 33 male patients with alcohol dependence as per DSM-IV criteria and 13 healthy controls were enrolled for the study. Regional measures of cortical cerebral blood flow were assessed using a high resolution Tc-99m-HMPAO single photon emission computed tomography (SPECT). Alcoholic subjects were divided into two groups according to onset of problematic alcohol drinking age.

Results: When three groups were compared, r-CBF differences were obtained in inferior frontal, inferior temporal, inferior left occipital and middle left frontal regions. Decreased r-CBF values were found in LO group when they compared to controls in both lower frontal and temporal regions ($p<0.05$). LO group showed significant reduced r-CBF values in regions of inferior frontal and temporal, inferior left occipital and middle left frontal when compared with EO.

Conclusion: Our findings revealed that, there were differences in r-CBF values in EO and LO alcoholics at early abstinence period. These findings suggest that frontal lobes have a key role in alcoholism neurobiology, as noted in previous studies. Repeating the measurements after a long-term abstinence will be useful in revealing differences among the alcoholic groups.

Keywords: Alcoholism, SPECT, Cerebral blood flow

Öz

Amaç: Alkol bağımlılığının beynin yapısı ve işlevselliği üzerinde olumsuz etkileri vardır. Alkole başlangıç yaşı, alkol bağımlılarının gruplandırılmasında önemli bir parametredir. Bu çalışmanın amacı erken (EB) ve geç başlangıçlı (GB) alkol bağımlılarında bölgesel beyin kan akımı (b-BKA) değerlerlerinin farklılık gösterip göstermediğini karşılaştırmaktır.

Yöntemler: DSM-IV ölçütlerine gore alkol bağımlılğı tanısı olan 33 erkek hasta ve 13 sağlıklı control çalışmaya alınmıştır. Kortikal serebral kan akımının bölgesel değerleri yüksek çözünürlüklü Tc-99m-HMPA tek foton emisyon bilgisayarlı tomografi kullanılarak değerlendirilmiştir. Alkolik olgular sorunlu alkol başlangıç yaşına göre iki gruba ayrılmıştır.

Bulgular: Üç grup karşılaştırıldığında alt frontal, alt temporal, alt sol oksipital ve orta sol frontal bölgelerde b-BKA farklılıkları saptanmıştır ($p<0.05$). GB grupta control grubuna göre her iki alt frontal ve temporal bölgede azalmış b-BKA değerleri bulunmuştur ($p<0.005$). GB grup EB grupla karşılaştırıldığında, alt frontal ve temporal, alt sol oksipital ve orta sol frontal bölgelerde anlamlı derecede azalmış b-BKA değerleri göstermiştir ($p<0.05$).

Sonuç: Bulgularımız erken ayıklık dönemindeki EB ve GB alkol bağımlılarında b-BKA'nda farklılıklar olduğunu ortaya koymuştur. Bu bulgular daha önceki çalışmalarda da belirtildiği üzere frontal lobun alkolizmin nörobiyolojisinde kilit role sahip olduğuna işaret etmektedir. Uzun sureli ayıklık döneminden sonra ölçümlerin tekrarlanması alkol bağımlısı gruplar arasındaki farklılıkların ortaya konmasında yararlı olacaktır.

Anahtar kelimeler: Alkolizm, SPECT, Serebral kan akımı

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Introduction

Alcoholism is a major public health problem in the world from both social and economic points of view. The adverse effects of alcohol abuse on human brain morphology, blood flow, metabolism, and neurocognition are well documented in the medical literature [1]. Functional neuroimaging studies in alcoholics have shown that global cerebral metabolic or perfusion defects mainly in the frontal regions without neurological diseases [2-5]. Among many significant findings from the literature studies on regional cerebral bood flow (r-CBF) of alcoholics, the most consistent one seems to be frontal hypoperfusion, although other cortical regions are also affected [3,6-9]. Whether these changes developed as a result of alcohol use or they have existed from the beginning has been discussed. Widespread bilateral reductions in white matter integrity were observed in abstinent alcoholics. The left inferior frontal gyrus was associated with drinking severity [10]. Binge drinking and withdrawal symptoms have been associated with the greatest neural abnormalities, particularly in frontal, parietal, and temporal regions [11]. Some studies have also reported that brain metabolism is increased during withdrawal period from alcohol [7,12]. There are also studies reporting that cerebral hypoperfusion improves in long-term abstinent alcoholics [13].

Advances of neuroimaging technology have allowed neurobiological theories and clinical heterogeneity of alcoholism to become better understood. Efforts to distinguish alcoholic patients into different subtypes are not new in the clinical field [14]. The classification system of Cloninger et al. and Knorring et al. are most approval and similar however have some differences [15-17]. Cloninger et al. suggested the existence of Type 1 and 2 alcoholism as different alcoholism subtypes [15]. Type 1 alcoholic patient's characteristics are late onset, moderate drinking behavior, less psychosocial problems and good prognosis. In contrast, type 2 alcoholics have more alcohol related problems, early onset of alcohol abuse (before twenties), family history of alcoholism, antisocial personality trait, affective disorder, genetic predisposition and poor psychosocial functioning [17]. The age of onset of alcohol abuse was the most significant finding in several classification studies [17,18]. The aim of the present study was to examine a possible differentiating pattern of regional cerebral blood flow (r-CBF) in patients with early and late onset alcoholism. In doing this, we intended to assess whether subdivisions of alcoholic populations based on age of onset to alcohol abuse is accompanied by different cerebral blood blow changes.

Materials and methods

The study was approved by local Ethics Committee (5.28.2012/007.2002). Subjects signed a written informed consent form. Thirty-three male patients of DSM-IV diagnosis of alcohol dependence and 13 healthy individuals were included in the study. Patients who had a severe physical illness, history of psychotic disorder, any evidence of an organic mental disorder, history of substance abuse (apart from nicotine) in the year before their admission to the hospital, or symptoms of any major affective disorder were excluded from the study. Lifetime severity of drinking problems was assessed by the Michigan Alcoholism Screening Test (MAST) [19]. Depression and anxiety levels were measured with Hamilton Depression Rating Scale (HDRS) and Hamilton Anxiety Rating Scale (HARS) [20,21]. The patients who started alcohol abuse before 20 years of age were classified as 'early onset' (EO, n=18) while those who began alcohol abuse after the age of 20 were grouped as 'late onset' (LO, n=15). In addition, at least two instances of social complications of alcoholism had to have been reported for the time before the age of 20 (such as job loss, alcohol related absence from school or work, arrest for intoxicated behavior, or violence while intoxicated). For the control group, 13 healthy males were selected on similarity to the patients in age, handedness and gender. Exclusion criteria comprised of neurologic/psychiatric illnesses, history of cardiovascular or endocrinological disorders and history of severe head trauma.

r-CBF measurement

r-CBF images were obtained by Single Photon Emission Computed Tomography (SPECT) using Tc-99m-HMPAO (hexamethyl propylene amine oxide). The measurements of r-CBF were performed at the end of a seven-day drug-free period and at the sixth and seven weeks of admission to the hospital. SPECT scans were enumerated randomly, and the clinical information was prepared by a blinded nuclear medicine expert. High-resolution SPECT was performed with double-capped Siemens e-cam camera (Siemens, Gerfahldt, Germany). The radioactivity distribution in the brain was recorded in a circular universe as 128 x 128 matrix 60 minutes after the administration of radioactive isotope. Reconstruction procedure was carried out using Butterworth filter (cut-off frequency 0.27 Nyquist, order 7) in Icon (Siemens) computer system, and fixed attenuation correction was performed with Chang method.

Visual analysis

Standard three dimensional cross-sections were examined. Perfusion defect was assessed in accordance with the criteria that contain observing more than 10% of asymmetry, wider reduced perfusion area than one or several sections, and observing the same defect in more than one plan [22].

Semiquantitative analysis:

In the horizontal sections obtained by grounding on orbitomeatal (OM) line, the images that are over approximately 33mm, 49.5 mm and 66 mm of the OM line were used for numerical calculation [23] (Figure 1). Cortex limits in selected cross-sections were determined through semi-automatic program, and the enumerations in the region of interest (ROI) were recorded as average enumeration. 6 pieces of ROI were placed in both sections [24] (Figure 2).

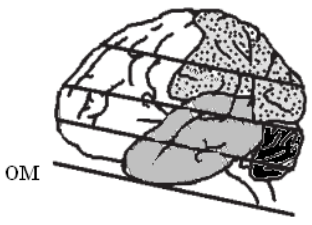

Figure 1: Schematic illustration of transaxial SPECT slices which are parallel to orbitomeatal line

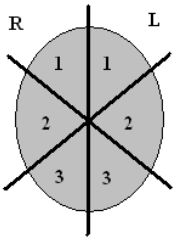

Figure 2: Schematic illustration of the regions of interest over a transaxial slice

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) for Windows, Version 18.0 software. r-CBF compared by one-way analysis of variance and Kruskal-Wallis analysis. Mann-Whitney U test was applied to dually compare the data of EO, LO and the control group with each other. Differences were considered to be significant if $p<0.05$.

Results

There were no statistically significant differences between the study groups in terms of age and gender. The average age of onset of alcohol abuse was 15.5±2.1 years in EO group and 24.8±4.7 years in LO group, the difference between groups was statistically significant (z=-4,790, p<0.001). Differences between groups in terms of total duration of dependence, age of first treatment admission, amount of daily alcohol intake were not statistically significant. There was statistically no significant difference between the MAST scores of the EO and LO alcoholics (z=-1.123, p=0.432). The depression scores of EO and LO groups in the abstinence period were found to be similar (EO=7.5±6.2, LO=6.4±3.2; z=0.000, p=1.000). Anxiety scores of both groups were not different from each other (EO=18,7±5.3; LO=17.5±3.8 z=-1.609, p=0.345). Table 1 shows sociodemographic and clinical characteristics of EO and LO groups.

Table 1: Sociodemographic and clinical characteristics of EO and LO Alcohol Dependents

	EO n:18 mean±SD	LO n=15 mean±SD	z	p
Age	38.9±9.7	43.9±7.6	-1.789	0.067
Education (year)	8.9±3.8	10.6±3.7	-2.046	0.047*
Age of onset of alcohol abuse (year)	15.5±2.1	24.8±4.7	-4.790	<0.001*
Age of first treatment admission (year)	37.2±5.9	43.2±10.8	-2.023	0.53
Daily alcohol intake (standard drink/day)	17.1±4.9	14.7±3.9	-1.890	0.23
Total duration of dependence (year)	14.5±6.4	13.2±4.8	-0.987	0.64
MAST	34.3±5.9	29.7±4.3	-1.123	0.432
HDRS	7.5±6.2	6.4±3.2	0.000	1.000
HARS	18.7±5.3	17.5±3.8	-1.609	0.345

EO: Early onset, LO: Late onset, Mann Whitney U testi, *p<0.05=statistically significant beween groups, SDd: standart deviation, MAST: Michigan Alcoholism Screening Test, HDRS: Hamilton Depression Rating Scale, HARS: Hamiton Anxiety Rating Scale

The relative perfusion rates of the groups are presented in Table 2. There were statistically significant differences in mean r-CBF in inferior frontal and temporal, inferior left occipital and middle left frontal regions. Compared with the results of control subjects, relative perfusion was significantly decreased in inferior frontal and temporal regions in the LO group (x2 =6.016, df=2, p=0.049) (Table 2). Decreased perfusion rates were determined in LO alcoholics in the inferior frontal-temporal-left occipital, middle left frontal regions, in comparison to those of EO group. There were no statistically significant differences in mean r-CBF between EO alcoholics and control group.

Discussion

Our study shows that especially regions of frontal and temporal lobes in both hemispheres are more affected in the early abstinence period. Our results support evidences of frontal system abnormalities in abstinent alcoholic subjects [25,26]. r-CBF values were different among the EO and LO alcoholics in the present study. In the light of these results, problematic drinking age may be a differentiating pattern in grouping alcoholism at the short-term abstinence period. There was no difference in the severity of alcoholism and period of abstinence among the groups in our study, but the early onset group had been exposed to toxic effects of alcohol for a longer period of time. Although there is no difference in terms of alcohol consumption intensity, the doses of benzodiazepines in first weeks of treatment and duration of detoxification period were higher in EO alcoholics than the LO group. Studies with r-CBF values in different alcoholic subgroups revealed inconsistent results. Tutus et al. reported that observed frontal lobe perfusion deficits in neuroimaging studies might be transistory in withdrawal period, but contrast to this suggestion data in long term abstinent alcoholics have shown perfusion defects [7,27].

Table 2: Comparison of r-CBF among three groups

r-CBF		EO n=18 mean±SD			LO n=15 mean±SD			Control n=13 mean±SD			Anova Test Kruskall Wallis x^2	df	P
Inferior slices	Right frontal	110.8	±	28.9	88.6	±	22.5	112.5	±	22.6	8.166	2	0.017* a,b
	Left frontal	109.4	±	28.4	88.0	±	26.4	111.2	±	22.3	7.723	2	0.021* a,b
	Right temporal	115.9	±	31.7	96.2	±	23.1	117.3	±	16.9	7.819	2	0,020* a,b
	Left temporal	115.1	±	28.9	95.6	±	26.0	117.7	±	16.7	7.957	2	0,019* a,b
	Right occipital	118.8	±	29.5	101.1	±	26.9	111.1	±	13.8	4.293	2	0.177
	left occipital	121.1	±	28.9	101.3	±	26.7	111.2	±	13.5	6.531	2	0.038* a
Middle slices	Right frontal	119.6	±	30.1	98.4	±	25.7	107.3	±	16.2	5.901	2	0.052
	Left frontal	118.1	±	28.7	95.2	±	28.0	106.1	±	17.4	6.878	2	0.032*a
	Right parietal	116.6	±	29.6	97.8	±	26.4	107.8	±	18.1	3.718	2	0.156
	Left parietal	117.3	±	29.2	97.5	±	27.7	107.5	±	15.4	5.368	2	0.068
	Right occipital	117.1	±	29.0	99.4	±	27.2	105.1	±	14.4	4.157	2	0.125
	Left occipital	117.1	±	28.2	99.0	±	27.1	106.0	±	15.3	5.644	2	0.059
	Right frontal	114.6	±	28.8	98.0	±	25.4	103.5	±	18.2	4.004	2	0.135
Upper slices	Left frontal	113.0	±	28.2	95.0	±	26.7	104.4	±	14.5	5.274	2	0.072
	Right parietal	109.5	±	27.5	96.2	±	25.2	102.3	±	16.4	2.923	2	0.232
	Left parietal	110.7	±	27.1	94.6	±	26.7	103.3	±	18.1	4.453	2	0.108
	Right posterior parietal	113.6	±	29.2	98.7	±	27.7	106.4	±	18.0	2,667	2	0,264
	Left posterior parietal	113.2	±	27.7	96.8	±	25.3	103.0	±	18.0	4.741	2	0,093

r-CBF: regional Cerebral Blood Flow, SD=standad deviation, *Kruskal wallis test p<0.05=statistically significant difference between three groups.
Post Hoc Test Multiple Comparisons results: a: LO group has statistically significant difference compared to EO (p<0.05), b: LO group has statistically significant difference compared to control (p<0.05)

Demir et al. reported SPECT results of EO versus LO alcoholics were not different each other but r-CBF values of EO and LO alcoholics were statistically different than the control subjects. Perfusion defect was found in left superior frontal region in the EO group by Demir et al [3]. In our study, in contrast to EO alcoholics, LO alcoholics showed inferior occipital brain area perfusion defect. As the LO group is considered to be older, depending on the effect of aging on the brain, hypoperfusion in posterior brain area like cerebellum and occipital lob may occur in alcoholism [28].

Evaluation of changes in the volumes of cerebral tissue and spinal fluid revealed that brain tissue recovery in the first month of the soberness is faster than the following 12 months. [29,30]. The fastest brain tissue recovery was observed in sober individuals with the highest drinking intensity and basal brain reduction. In the rapid return of the brain tissue recovery, sober periods were found to be effective. This can be interpreted as explanatory for the close results of EO group with control group in terms of regional cerebral blood flow at the end of the second month. In another study evaluating alcoholics in the early abstinence period and after 12 months showed that the abstinent subjects and control group are not different from each other in terms of frontal and parietal grey matter perfusion [31].

We have used the age of onset to alcohol abuse as a more significant biological determinant in our study. It is evident from comparative studies that all different classification approaches suffer from potential diagnostic imprecision or overlap problems. In our study, we wonder why LO group could not reach normal r-CBF values in the early abstinence period. Is the older age of this group a factor in terms of neuroplasticity? We think that perfusion deficits of some regions may be a transient finding in abstinence. These changes may reflect a metabolic state related to termination of alcohol, or a general brain metabolic change in chronic alcoholics. The longitudinal literature studies in neuroimaging area did not classify alcoholics into groups according to the age of onset.

It is now well-known that alcohol causes widespread effects on central nervous system. Recent neurophysiological studies show that there is a compensatory re-organization of the brain system in alcoholics balancing the frontal lobe dysfunctions. The alcoholic brain damage is consistently shown to be reversible in both structural and functional studies and latest techniques point out to an active regeneration process in different alcoholic groups which seems to be an important encouraging factor for treatment modalities. Female cases were not included in our study, because these are low in rate in clinical practice. Obtained results should be interpreted as preliminary since the number of cases in both groups is low. In addition, another limitation in our study is the fact that basal cerebral blood flow values of both groups were not measured. The fact that we could not perform longitudinal measurement in the longtime abstinence period is another limitation. Performing neuroimaging studies evaluating brain functions in alcoholics that are long-standing soberness, involving both genders, will be valuable for the scientific literature. In literature, there are no studies on cerebral blood flow apart from the study of Demir et al. which was conducted by classifying the dependents according to the age of onset [3]. In this sense, our study is valuable. The degree of neurobiological anomalies following acute detoxification and the flexibility of recovery during abstinence are not only affected by existing comorbid situations (cigarette, mood disorders, hypertension, etc.), but they are also affected by genotype. The support of multi-dimensional diagrams and classifications with brain imaging and genetic studies will provide support for the endophenotypes that distinguishes alcoholism. We believe that this study will shed light on further clinical studies with larger sampling.

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