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Research Peper: Brain Structure Changes Associated With Methamphetamine Abuse in Brain Magnetic Resonance Imaging

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ABSTRACT

Background: Amphetamines constitute a group of central nervous system stimulators with an increasing frequency of usage and destructive outcomes on the metabolism, perfusion, and structure of the brain. This study aimed at evaluating the structural brain changes following amphetamines abuse, using Magnetic Resonance Imaging (MRI).

Methods: This cross sectional study was conducted on the individuals, who were admitted to the toxicology Emergency Room (ER) with continuous amphetamines abuse for at least six months and a positive methamphetamine urine test. Positive Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for dependency and addiction to methamphetamine were also considered as the inclusion criteria. Following informed consent, the demographic information, and data on methamphetamine use were collected. An MRI was performed for all participants as soon as relative recovery. A matched control group also underwent MRI simultaneously.

Results: Forty male (20 cases of methamphetamine addicts and 20 healthy individuals) with a Mean±SD age of 28.1±5.11 years were investigated. The Mean±SD age of starting methamphetamine abuse was 25.6±10 years. About (75%), (n=15) of the patients abused methamphetamine 6-9 months, while others had abused it for more than 10 months. All cases used to abuse methamphetamine at least once a week, with (85%) of them inhaling it. The results showed that the only change in the brain MRI of methamphetamine abusers was hyperintensities increase in deep and periventricular white matter (only positive MRI in 3 cases, P=0.231). Oral consumption and higher doses had induced greater changes in the brain structure.

Conclusion: Methamphetamine dependency may increase deep and periventricular white matter hyperintensities.

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1. Introduction

Having similar structure and effects, amphetamines were first produced in 1887 with the synthesis of amphetamine (1-methyl-2-phenethylamine) and methamphetamine, 3-4-methylenedioxymethamphetamine (MDMA), and other members of this family [1]. These drugs increase the neuronal network activity by expanding the synoptic area of biogenic, dopamine, norepinephrine, and serotonin amines [1-3]. A report in 2010 estimated that 13.7-52.9 million people had used amphetamines at least once a year [4]. In 2011, it was reported that amphetamines were the most widely used stimulant drugs after cannabis in Europe with a prevalence of (2.3%) among schoolgirls under 18 years [5, 6]. Evidence from previous studies suggests that amphetamines users face the risk of serious brain disorders in terms of perfusion, metabolism, and structure [7-10].

Recent studies have verified structural brain changes because of amphetamines such as the reduction in the volume of white matter, increased deep and periventricular White Matter Hyperintensities (WMH), disturbed fractional anisotropy measures in the right frontal lobe, and other white matter disorders in basal ganglia [11, 12]. Further studies have suggested the evidence of reduced gray matter in the limbic system, cingulate lobe, paralimbic cortex, the middle part of the frontal lobe gyrus, and the temporal lobe among amphetamine abusers compared to those of normal people [13-15]. Nevertheless, other studies in this area suggest no changes in the general brain structure and gray matter in amphetamine abusers compared to those of the non-users [16].

On the other hand, metabolic disorders can lead to the apoptosis of brain cells and a decrease in glial cells count. In addition, perfusion-related disorders in the brain can result in infarctions that will destroy valerian and cause axonal injury in gray matter [1]. These changes in the perfusion, metabolism, and white matter structure can potentially lead to primary or secondary brain disorders [17].

Given the destructive effects of amphetamines on the metabolism, perfusion, and structure of the brain, and since there has not been any MRI study in this context despite the increasing prevalence of amphetamines abuse in Iran, the current study was conducted to assess the structural brain changes in the MRI of methamphetamine abusers.

2. Materials and Methods

This was a two-group cross sectional study on patients with a minimum six-month history of methamphetamine abuse, who were admitted to the Emergency Department of Clinical Toxicology of Imam Reza University Hospital, Mashhad University of Medical Sciences, Iran, over six months.

Twenty cases, who met the inclusion criteria (at least six months of continuous methamphetamine abuse, positive urine toxicology screen for methamphetamine, positive DSM-IV criteria for dependency, and signed informed consent), were included. Individuals with positive HIV test, those suffering from chronic kidney and liver diseases, any contraindication of MRI, patients under psycho-medication or with other drugs addictions were excluded from the study.

Demographic information (age and sex) and methamphetamine abuse data including the age, in which the abuse was started, dosage, duration, and method of abuse were collected. Afterward, a urine sample for toxicology screening was taken to show the presence of methamphetamine consumption. In order to compare the brain structure of addicted individuals with that of healthy people, a sexually homogeneous group was selected as control. Control group contained 20 healthy volunteer cases without the history of methamphetamine use and negative urine test for methamphetamine (The personnel of poisoning ward).

Radiological findings

A brain MRI was taken at the time of admission in poisoning ward and just before discharge (Each patient underwent MRI twice), using Siemens Symphony in axial T1 and T2 and diffusion-weighted and in sagittal T1 and T2 and diffusion-weighted sections. All the recorded images were interpreted by a professional radiologist (The radiologist evaluation was blind), and if any pathology was observed, neurology consult would be performed (Only for patients with signs of Intracranial Pressure "ICP" increasing). The findings of MRI included changes in the white matter volume, increased hyperintensities in deep and periventricular white matter, changes in the gray matter in syngolite, limbic and paralimbic cortex lobes, and changes in the volume of globus pallidus, putamen, and the mid-posterior section of the corpus callosum.

Data analysis and statistical procedures

SPSS V. 16 was used for analysis. We evaluated the normal distribution of data by the Kolmogorov-Smirnov test. The mean and standard deviation were applied for normal continues variables and median and Interquartile Range (IQR) was used for non-normally distributed data. On the basis of the normal distribution of data, independent samples t-test or Mann-Whitney U test was used for difference between two groups. The Fisher's exact-test was used to differentiate frequencies between two groups. The significance level for all of the mentioned tests was applied at (0.05) and data were analyzed by SPSS V. 17 software.

3. Results

During the six-month course of the study, 34 suspected male cases of amphetamine overdose, who had been admitted to the toxicology emergency department of Imam Reza University Hospital, participated in this study; 14 of these cases were excluded based on the inclusion and exclusion criteria; five of them lacked the inclusion criteria, two were HIV positive, four had simultaneous chronic kidney or liver diseases, and three were addicted to other drugs. The results for 20 patients and 20 healthy adults were analyzed at the end.

In this study, 40 male participants with the Mean±SD age of 28.1±5.11 were assigned to two groups. There were no significant age or sex differences between the two groups. The Mean±SD age in the case and the control groups was 26.85±6.56 and 29.15±3.15 (P=0.114), respectively.

The lowest age to begin methamphetamine abuse was 17 and the highest was 37 (with a mean of 25.6). Eleven cases (55%) had abused the drug for 6 to 7 months, while this value was 8-9 months in four cases (20%), 10-12 months in two cases (10%), 13-24 months in one case (5%), and more than 24 months in 2 cases (10%). All cases had abused the drug at least once a week. The method of drug abuse was snuffing in 17(85%) and oral consumption in 3(15%) cases.

The findings of MRI indicated no changes in the white matter volume, the gray matter of syngolite, limbic and paralimbic cortex lobes, and the volume of globus pallidus, putamen, and a mid-posterior section of the corpus callosum in those with methamphetamine dependency. The control group had a normal MRI.

Only in three cases (15%), increased deep and periventricular white matter signal intensities was seen, which was absent in the rest of the patients (85%).

4. Discussion

This study shows that methamphetamine abuse can increase deep and periventricular white matter signal intensities. Deep and periventricular WMH could be described as patchy changes or white matter perfusion in the MRI based on T2 [18]. According to the results of this study, it can be hypothesized that aside from all other proven side effects, methamphetamine abuse can cause brain structure damage.

Previous studies have suggested that methamphetamine abuse can lead to a decrease in the level of N-acetylaspartate and frontal glucose metabolism [19]. The reason for increased deep WMH is possibly brain ischemia, although increased periventricular WMH is less investigated [20]. Nonetheless, it seems that aging, mild syncope, multiple sclerosis, and related complications can cause increased periventricular WMH [21].

With regard to our patients' age and conditions, the most relevant cause might be a mild syncope during methamphetamine abuse. Thus, vascular mechanisms are the leading causes of rising WMH in patients with methamphetamine dependency [10, 22]. In an investigation performed by Bae et al. [23], prevalence, intensity, and the locality of T2-weighted MRI of white matter signal hyperintensities in 33 methamphetamine-dependent patients were studied. The results of this study indicated that WMH was significantly more prevalent in those who were methamphetamine-dependent.

Another noteworthy finding in the present study is the correlation between methamphetamine dosage and the probability of WMH occurrence in the abusers. Based on the results of the present study, the chance of coming across a pathological observation is greater in oral amphetamine abusers (although it is not a common route of methamphetamine use). Given the significantly limited number of observations, the correlation between the method of abuse and pathologic findings cannot be confirmed, and further studies with larger populations are required.

The correlation between methamphetamine dosage and structural disorders was among other findings, which was only positive for white matter signal hyperintensities. Nevertheless, because of the small study population, it was not possible to determine the most effective dose. In contrast to our study, a research reported a

significant correlation between methamphetamine dosage and white matter signal hyperintensities [23].

All of our affected patients were men, perhaps because of a protective role of estrogen against brain structural disorders following methamphetamine abuse, which has been suggested by many studies [12, 20, 23-25]. In contradiction, another study has shown that men probably do not benefit from the protective features of estrogen in brain veins [26]. What threatens methamphetamine abusers is developing behavioral disorders such as depression, panic and bipolar disorders, and schizophrenia, in which cases a rise in WMH has been reported [27-29].

This study also shows no change in white and gray matter volumes in cingulate, limbic, and paralimbic cortex lobes in the MRI of the experimental group. On the other hand, there were no volume changes in globus pallidus or putamen in methamphetamine-dependent cases in comparison to the control group. The possible causes of this observation can be developmental time-courses, gender difference, the severity of methamphetamine abuse, and abstinence duration [29, 30]. In other studies, no changes in white and gray matter were reported [15, 31, 32].

In a study by Thompson et al. no significant changes of gray matter were reported in methamphetamine abuse; while, there was a severe decrease in the gray matter of syngolite, limbic, and paralimbic cortex lobes in those who were methamphetamine-dependent [15]. In a study by Change et al., no changes were observed in total brain volume in both experimental and control groups [28]. However, globus pallidus and putamen were much bigger in those with methamphetamine dependency compared with the control group, and the mid-posterior section of the corpus callosum was larger in women; it is possibly because of gliosis and inflammatory response to brain trauma following amphetamine abuse. Similarly, Oh et al. reported no changes in the volume of the corpus callosum [32].

In a survey by Lawyer et al., no difference in the thickness of gray matter was found between the amphetamine users, who simultaneously consumed little alcohol and those who were not alcohol consumers with that of the control group [16]. The only difference existed in the right upper frontal cortex thickness and left the central blade in long-term alcohol users, which was considerably lower compared to healthy people. As a result, amphetamine abuse does not affect brain cortex thickness except in individuals with simultaneous alcoholism.

The minimum age to begin methamphetamine abuse was 17 and the maximum age was 37, showing that most methamphetamine abusers were in the most vulnerable age for addiction [33]. In similar studies, the age of participants ranged between 25 and 45 [23, 25, 26, 29, 30, 34-36].

The simultaneous use of other substances can be mentioned as another reason for the minimal change of brain structure in methamphetamine abuser cases [12]. On the other hand, background diagnostic disorders could inflict structural changes in the brain that are sometimes different from amphetamine-induced changes [37].

The dosage and duration of amphetamine abuse can also affect the intensity of structural brain disorders [38]. However, some studies have recorded the importance of the number of times in a day that the drug is abused and not its dosage [29]. In the present study, the number of daily or weekly uses and its effects on structural brain disorders in the MRI are given regardless of dosage. The results have shown no significant correlation between the duration of amphetamine abuse and structural changes, which could be the result of limited sample size. The most important point in a review on all related studies is the period, in which the drug was not abused, and the correlation of this phenomenon to the structural disorders, which has not been investigated herein [14, 23, 31].

To the best of our knowledge, this is the first Iranian study that evaluates the brain MRI changes in amphetamine abusers. The first limitation of this study was group matching. Despite attempts to homogenize the two groups in terms of age and gender, other factors such as diagnostic and behavioral disorders, smoking, and alcoholism should be taken into account. On the other hand, the small sample population led to vague answers to some questions and hypotheses; for instance, the results showed that the structural brain changes were correlated to the weekly frequency of abuse. However, how much of these effects are dose-related still remains unclear and could not be determined because of the small number of people in weekly use patterns. Thus, further studies are suggested to assess drug dosage in inflicting structural brain changes with controlled confounding variables.

The cross sectional design of this study is another limitation and it is recommended that a prospective study be designed in two groups including amphetamine abuser and non-abusers to reach a more realistic interpretation of the structural brain changes while controlling the confounding variables.

5. Conclusion

Methamphetamine abuse may increase deep and periventricular WMH. More investigations with larger sample size are recommended for better interpreting of the structural brain changes in methamphetamine abusers.

Ethical Considerations

Compliance with ethical guidelines

This study was ethically approved by the Ethics Committee of Mashhad University of Medical Sciences (No. IR.mums.rec.910338).

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Author's contributions

All authors contributed in designing, running, and writing all parts of the article.

Conflict of interest

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