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Research Article

## Frontal Executive Functions in Medication Overuse Headache

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### Abstract

**Objective**: In the neuroimaging studies, prefrontal dysfunctions have been reported in the patients with medication overuse headache (MOH). The study investigates the presence of cognitive deficits in patients with MOH or migraine without aura as compared to healthy controls.

**Methods:** Neuropsychological test battery assessing frontal executive functions and attention was applied in 50 patients with MOH, 50 patients with migraine without aura and 50 control subjects. Depressive symptoms were measured with Hamilton depression rating scale.

**Results:** The results were compared between the three groups using analysis of covariance. Tukey test was used for post hoc multiple comparisons. The patients with MOH performed worse than patients with migraine on the digit span-forward, digit span-backward, verbal fluency KAS, animal numbers in attention and total categories completed on Wisconsin card sorting test (WCST), Trail making test A-B (TMT A-B), total number of errors on Continuous performance test (CPT) in executive functions whereas they were worsen than the control subjects on almost all tests. The patients with migraine were significantly poorer than control subjects on digit span-backward, and showed higher number of perseverating responses on WCST, total number of errors on CPT, and total number of errors on Go-NoGo.

**Conclusion:** The patients with MOH have frontal dysexecutive syndrome characterized by an inability in the inhibition of inappropriate responses and attention deficit. There are studies suggesting an association between drug addiction behavior and MOH via prefrontal cortex involvement. Our results further support the notion that MOH may be a part of the spectrum of drug addiction behavior.

**Keywords:** Medication Overuse Headache; Migraine; Cognitive Function

## Introduction

Migraine is the second most common cause of the primary headache after tension-type headache. It is characterized by generally unilateral attacks lasting 4-72 hours, presenting as throbbing headaches. It is unclear whether the cognitive impairment is a clinical feature of migraine. Many migraine patients report subjective cognitive impairments such as forgetfulness, inattentiveness and psychomotor tiredness [1]. The studies comparing the neuropsychological test performance of the patients with migraine to that of control subjects showed discrepant findings [1-4]. Some studies demonstrated impairments in working memory, executive functions, language, reaction time, attention, as well as deficits in visual processing, concentration, information speed processing. There are also many brain neuroimaging and electrophysiological studies that support findings of these studies. In a SPECT study, Calandre et al [1]. showed brain perfusion abnormalities in multiple cortical areas and poorer neuropsychological performance in tests measuring verbal and visual memory[1]. Evers et al. reported a loss of cognitive habituation and an increased cognitive possessing time on measures of event-related potentials in the patients with migraine [2,3]. However, there are some studies found no differences in cognitive status between patients with and without migraine. Gaist et al. investigated the long term effects of migraine on cognitive functions in a large population base sample of middle-aged twins and showed no cognitive deficits in the patients with migraine as compared with migraine-free controls [4]. Pearson et al. compared older patients with migraine with matched controls on four measures cognitive ability, in blinded design and reported that there are no significant differences between patient and control groups [5].

Medication overuse headache (MOH) is a chronic headache that almost exclusively results from the excessive use of migraine-specific drugs such as triptans and ergots, as well as opioids, nonsteroidal anti-inflammatory analgesics, combined analgesics (barbiturate or caffeine) in patients with a primary headache disorder. The primary headache in such patients is predominantly the migraine or tension-type headache. According to the second edition of The International Classification of Headache Disease (ICHD-II), MOH is defined as a headache present on ≥ 15 days/month and with regular intake for >3 months of one or more drugs for acute and/or symptomatic headache treatment. In this definition, the continuing overuse of medication causes the headache to increase in severity but the headache resolves or returns to its baseline level around 2 months after the cessation of medication [6]. However, the IHCD-III (beta version) removed the criterion regarding resolution or reversion [7].

In patients with migraine or tension-type headache is unclear what factors trigger MOH [8,9]. Even though the patients with MOH are aware that the analgesics and/or migraine-specific drugs do not alleviate pain, they cannot suppress their drug intake [9,10]. MOH is virtually a vicious circle. The patients with other painful disorders as rheumatologic diseases that require frequent use of analgesics do not enter this vicious circle.

It may be hypothesized that such drugs present an inappropriate stimulus for the patients with MOH and the patients cannot inhibit the behavior associated with this inappropriate stimulus. The studies suggesting an association between substance dependence and MOH are in line with this hypothesis [9-13]. Therefore we hypothesize that one of the underlying mechanisms of MOH is a frontal executive dysfunction characterized by an inability to inhibit inappropriate response, stimulus dependence, and the impairment of set shifting.

We assessed attention and frontal executive functions in the patients with MOH and migraine by a neuropsychological test battery assessing specifically the frontal executive functions and attention, and compared these patients to control subjects in these measurements.

## Participants and methods

Patients and control subjects were both recruited consecutively from Headache Outpatient Clinics at Ondokuz Mayis University Medical School Department of Neurology and, Samsun Education and Research Hospital, Department of Neurology, in Samsun, Turkey. Consecutive 50 patients with migraine without aura and 50 patients with MOH were included. Patients with migraine without aura were diagnosed according to the ICHD-II criteria while the patients with MOH were diagnosed according to ICHD-III (beta version) criteria [6,7]. All patients with MOH were previously diagnosed as having either migraine or tension-type headaches. We have performed the psychiatric interview to exclude depression, generalized anxiety disorder, obsessive compulsive disorder or psychological abnormalities in personality. We have eliminated the patients with depression, generalized anxiety disorder, OCD, psychological abnormalities. Among the migraine and MOH patients, we included the ones without any confounding factors present as much as possible. There were no the patients with MOH who took opiates. All patients used simple analgesics, nonsteroidal anti inflammatory drugs or nonsteroidal anti inflammatory drugs with caffeine. The numbers of drugs were >5 per week for all patients. When MOH was diagnosed, we proposed to discontinue the drugs to the patients. Neuropsychological tests were performed 2 or 3 days after discontinuation. The patients classified the pain as mild, moderate and severe. Neuropsychological tests were performed in interictal headache period. The patients have had mild and moderate pain during neuropsychological testing. The control subjects were recruited among the relatives of the patients who visited our outpatient clinics for reasons other than headache and headache free.

None of the patients and control subjects had other neurologic and psychiatric, and systemic illnesses or history of head trau-

ma. Neurologic examination was normal for all participants. The demographic data of the patients and control subjects are presented in Table 1.

**Neuropsychological assessment**

Neuropsychological battery included tests assessing frontal executive functions and attention (Table 2). Frontal executive functions were examined using Wisconsin Card Sorting test (WCST), Stroop, computerized form of the Continuous Performance Test (CPT) and Go-NoGo, Trail Making Test (TMT) A-B. Attentional functions were assessed using Digit Span (forward-backward), and verbal fluency tests (K-A-S and Animal numbers/1 minute) [14-16].

WCST measures mental flexibility, abstraction, hypothesis testing, and the ability to alter responses based on feedback from responses It consists of four stimulus cards and 128 response cards. Each card comprises one of four forms that differ in color and number. The subject matches each stimulus card to response cards according to a specific rule. After 10 consecutive correct response, the examiner switches the rule without warning. When the subject completes the six categories or finishes 128 cards, the test is terminated [14-16].

In TMT A, the subject draws a line to connect the circles containing numbers from 1 to 25 in ascending order as quickly as possible. TMT B is more complex than TMT A because the task contains both numbers and letters. The subject should connect numbers (1-13) and letters (A-L) in an alternating order as quickly as possible. The time of completion of TMT A and B parts constitute the scores. The TMT A score reflects mainly visuoperceptual abilities whereas TMT B is an indicator of working memory, susceptibility to interference, and task-switching ability [14-16].

In digit span forward, the examiner reads a sequence of digits in one-second intervals and then the subject repeats in same order. In digit span backward, the subject repeats the numbers in reverse order [14-16].

In CPT, the subject is shown various letters on a computer monitor and asked to press a computer key when the target letter (A letter after letter Z) appeared on the computer monitor. Total corrects, total errors, omission and commission numbers are calculated. This test is measured the sustained attention ability [14-16].

In Go-NoGo test, the subject hears two different sounds. One of these sounds contain single signal, and the other one contains two signals. The subject must press a computer key when he/she hears the single signal but not two signals. Total corrects, total errors, omission and commission numbers are calculated. This test measures response inhibition ability [14-16].

Stroop test involves showing words that are the names of colors. The subject is asked to rapidly state the color of written word and ignore the written word itself. This test is a measure of resistance to interference, speed of information processing and the ability to inhibit inappropriate stimuli [14-16].

Verbal fluency is tested with phonemic fluency task and semantic fluency task. For phonemic fluency, the subject is asked to produce as many words as possible starting with K-A-S and for semantic fluency as many animal names as possible within a 1-minute interval [14-16].

Hamilton Depression Rating Scale (HDRS) was applied specifically to quantify the probable depressive symptomatology in both the patient and the control groups [17].

**Statistical Analysis**

Statistical analyses were performed with SSPS 16.0 statistical software (SSPS, Chicago, Illinois). The Kolmogorov-Smirnov test was applied to assess the normality of the neuropsychological test scores. Demographic and neuropsychological test scores, depression scores were normally distributed, except animal perseveration. These variables were compared between the three groups using analysis of covariance (ANCOVA). Tukey test was used for post-hoc multiple comparisons. Animal perseveration, a non-normal distributed, was compared with nonparametric Kruskal Wallis test. P value ≤0.05 were regarded to be statistically significant.

## Results

This study was performed in 50 patients with migraine without aura, 50 patients with MOH and 50 control subjects. Demographic features of patient groups and controls did not differ significantly (Table 1). The scores of neuropsychological tests were presented in Table 3. ANCOVA test demonstrated statistically significant differences between patients and control groups on all neuropsychological test except K-A-S perseveration, total number of correct responses on WCST, total number of correct responses on CPT. Turkey post-hoc multiple comparisons showed that patients with MOH were worse than patients with migraine on the digit span forward, digit span-backward, verbal fluency tasks and total categories completed on WCST, TMT A-B, total number of errors on CPT.

The patients with migraine performed significantly poorer than control subjects on digit span-backward, and showed higher number of perseverating responses on WCST, total number of errors on CPT, and total number of errors on Go-NoGo. There were also statistically significant differences between the patients with MOH and control subjects on all neuropsychological tests except for a few subtests (K-A-S perseveration, total number of correct responses on WCST, and total number of correct responses, omission and commission on CPT).

In addition, HDRS scores of both patients with migraine and MOH were significantly higher than control subjects whereas there was no difference between the two patient groups. The presence of depression may have a negative impact on performance on neuropsychological tests. However, the depression in the patient groups was still below the criterion for clinical depression. After controlling for depression scores, we saw that statistical analysis results remained the same, indicating that depression does not present a confound in the study.

## Discussion

Although the level of performances in all of the neuropsychological tests were lower in the patients with migraine than those of control subjects, the differences in some of the tests reached statistical significance. These results suggest that attention and executive functions in the patients with migraine, even if lightly, impaired than those of control subjects.

In literature, there are many studies investigating the neuropsychological performance in patients with migraine. The results of these studies are somewhat in conflict. A recent study using elderly patients with migraine did not show a meaningful relationship between migraine and cognitive decline [18]. In Maastricht Aging Study, a longitudinal population-based study, authors assessed cognitive functions in patients with migraine at the baseline and six years later using MMSE, immediate and delayed recall tests, and tests for simple and complex speed. They found that migraine headaches and the use of any migraine medication have no effect on any cognitive measures [19]. However, a number of studies showed mild or moderate cognitive deficits in the patients with migraine [20-23]. Farmer et al. revealed reductions in working memory, reaction times, concentration and visual spatial processing in migraineurs [21]. Mongini et al. pointed out a possible relationship between chronic migraine and dorsolateral and orbitofrontal prefontal dysfunctions [22]. This relationship was found to be partly independent of the patient's psychological traits and psychiatric disorders. Schmitz et al. showed that migraineurs, compared to control subjects showed decreased frontal and parietal lobe grey matter density and executive dysfunction [23]. We found only poorer performance on digit span backward, number of perseverating responses in WCST and total number of errors on CPT test in patients with migraine. These tests are predominantly sensitive for the cognitive functions subserved by the prefrontal cortex [14-16]. The results of our study agree with the studies showing mild attention and executive dysfunction in patients with migraine.

Our study showed that the patients with MOH were significantly worse from control subject on almost all neuropsychological tests except a few subtests. Although the scores in these subtests were worse in the patients with MOH compared to control subjects, the differences in the test scores did not reach statistical significance. In additional, there were significant differences between patients with MOH and patients with migraine on a number of tests assessing attention and executive functions.

The etiopathological mechanisms of MOH remain unknown. Despite the evidence of genetic, neurophysiological, neuroendocrine, psychological abnormalities, there is still no unique explanation for the mechanisms underlying of MOH in the literature.

Very recently, Biagianti et al. published the first study that assessed whether there is a decision-making deficit in patients with MOH [11]. The authors examined twenty patients with MOH and monitored for any relapse into medication overuse had 12 months of follow-up. They used the Structured Clinical Interview for DSM-IV TR Axis II Personality Disorders, Anxiety and Depression Hamilton Scales, Severity of Dependence Scale for the psychiatric examination, the migraine disability assessment questionnaire for the neurological examination, and Iowa gambling task (IGT) for neuropsychological assessment. At 12-months follow up, the neurological and psychiatric examination recovered to normal but the deficit in IGT performance persisted demonstrating an impairment in decision-making.

It has been considered that the decision making ability has a distinct anatomic substrate (ventromedial prefrontal cortex), than other frontal executive functions (dorsolateral and orbitofrontal prefrontal cortex). IGT is known to be a succesful measure of decision making and task-sensitive functions of the ventromedial portion of the prefrontal cortex [24,26].

In the present study we used the neuropsychological tests predominantly evaluating dorsolateral and orbitofrontal prefrontal cortex functions. These functions include working memory, selective attention, mental flexibility, set-shifting, judgment, inhibition of inappropriate response, reasoning, abstraction, susceptibility to interference, so on [14-16]. Especially, on WCST, Stroop test, Go/NoGo task, the patients with the frontal dysexecutive syndrome performed worse. Our results demonstrate that the patients with MOH are unable to inhibit responses to inappropriate stimuli, set-shifting, and modify behaviour based on new information, in additional to being susceptible to interference, dependent to stimuli, perseverative. In this respect, the patients with MOH are partially similar to the patients with frontal dysexecutive syndrome. Our and Biagianti's findings suggest that the orbitofrontal, dorsolateral and ventromedial prefrontal executive functions are impaired in patients with MOH.

There are a few neuroimaging studies, demonstrated hypoactivity/hypometabolism in some components of the frontal executive functions network in the patients with MOH, supporting this opinion.

In a fMRI study, Grazzi et al. evaluated the patients suffering from chronic migraine with symptomatic medication overuse (CMwMO) before withdrawal and compared with those obtained headache-free period after withdrawal. They found the hypoactivation in the right supramarginal gyrus, the right inferior and superior parietal cortices before withdrawal whereas activity improved to normal 6 months after withdrawal. The supramarginal gyrus, and the right inferior and superior parietal cortices are the epicenters of frontal executive functions network [27].

Interestingly, an association has been found between MOH and orbitofrontal cortex dysfunction. Fumal et al. investigated 16 patients with MOH using $^{18}$F-fluoro-deoxyglucose PET before and 3 weeks after withdrawal therapy and compared the results to a PET data bank of healthy volunteers. Before the withdrawal therapy, they found that bilateral thalamus, OFC, anterior cingulate gyrus, insula/ventral striatum, and right inferior parietal lobule were hypometabolic while the cerebellum vermis was hypermetabolic. All metabolic areas recovered to almost normal glucose uptake after withdrawal therapy, except OFC where a further metabolic decrease was found [28].

In recent years, there are a number of studies that suggest some similarities between MOH and drug addiction [8-10,12,13,29,30]. Fuh et al. showed that 68% of 895 MOH patients met the DSM-IV criteria for drug dependence [13]. Radat et al. found that two-thirds of 247 MOH patients met DSM-IV criteria for dependence. Additionally, more dependent than nondependent MOH patients were dependent on psychoactive substances (17.6% vs. 6.1%) [10]. In a cross-sectional study, Grande et al. recruited the Severity of Dependence Scale (SDS) in 386 people with chronic tension-type headache from the general population and tested the hypothesis that SDS score is associated with a diagnosis of medication overuse. Among 386 people with chronic tension-type headache, 44% showed medication overuse. In people with medication overuse, mean SDS scores were significantly higher than those in people without medication overuse. According to these results, authors suggested that the SDS score was a significant predictor for medication overuse in people with chronic headache [30].

A deficit in decision making is an important feature of the drug addicts. Previous neuropsychological and neuroimaging studies have shown that there is an association between decision making deficits and prefrontal cortex dysfunction in the drug addicts [25,31-34]. Roger et al. compared the decision-making behavior of drug addicts, and patients with focal lesions of orbital prefrontal cortex (PFC) or dorsolateral/medial PFC. They found that drug addicts show similar decision-making deficits to those of the patient with focal damage to orbitofrontal prefrontal cortex [25]. In a PET study, Bolla et al. reported that cocaine abusers show persistent functional abnormalities in prefrontal neural networks involved in decision-making. These studies have demonstrated that there is an association between MOH and drug addiction behavior via prefrontal cortex [31].

In conclusion, the studies mentioned above and our results suggest that the neuropsychological profile of MOH is predominantly characterized by the frontal executive dysfunction. The prefrontal cortex dysfunction may play a role in the development of MOH. Due to similar the neuropsychological profile and anatomic substrate, MOH may be a part of the spectrum of drug addiction behavior or drug-dependence.

There are a number of the limitations of the present study. First, we did not use any formal-structured scale to assess the comorbidity in the patients and control groups excluding Hamilton depression scale and psychiatric interview. The anxiety, neuroticism, psychological abnormalities in personality are the potential confounds affecting the neuropsychological tests performances. Second, we did not quantitatively investigate a correlation between the neuropsychological test scores and the frequency, intensity of the headache and number of drugs per month.

Further research would benefit from more extensive investigation of potential confounds in understanding the cognitive profile of MOH.

## Conflicts of interest

Conflicts of interest the authors declare that they have no conflicts of interest.

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