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Topo-kinesthetic memory in chronic headaches. A new test for chronic patients: preliminary report

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Abstract The objective of this study was to establish if chronic headaches with medication overuse can modify a topo-kinesthetic memory test. Nineteen patients with medication overuse headache (MOH), 13 patients with chronic tension-type headache (CTTH) without medication use and a group of "normal" subjects underwent a topo-kinesthetic memory test at T0 and after one month (T1); a control group of healthy volunteers was also tested to establish the baseline in our experimental setting. After one month, in the MOH patients there was a reduction of medication overuse from 3.3±2.65 to 1.1±2.23 (p<0.01), but no significant reduction in headache frequency and severity index, quality of life, anxiety and depression scores. The navigation time at T0 was 14.3±4.97, 27.9±10.12, 34.3±15.38 and 7.5±2.33, 10.1±2.95, 11.4±3.21 for control, MOH and CTTH with closed and open eyes, respectively (p<0.02). At T1, the MOH patients reached performances with open eyes similar to the healthy controls, while with closed eyes the navigation test reached times similar to those of CTTH patients. The topo-kinesthetic memory test seems both able to discriminate MOH and CTTH from healthy volunteers and to be related to pain scores but is not influenced by the use of drugs.

Keywords Topo-kinesthetic test • Chronic tension-type headache • MOH

Introduction

It is well known that chronic headache patients complain of loss of concentration and memory disturbances and often doctors as well as patients attribute this impairment both to chronic pain and daily drug use.

Comorbidity between headache and other disorders such as psychological or memory problems is a topic of increasing scientific interest. A central neurogenic mechanism such as a dysregulation of some neurotransmitter system might underlie not only headache but also other coexistent disorders; findings highlight the role of serotonin pathways [1–3].

Savarese in 2000 evaluated the memory functions in 71 patients with chronic daily headache and showed a severe impairment in patients with chronic tension-type headache (CTTH), especially for visual-spatial memory, without relation to drug abuse, and suggested a serotonergic imbalance [4]. Afterwards, an abnormal cortical processing of nociceptive input in chronic migraine patients was suggested, which represents a typical chronic state of

pain. In both tension-type headache and chronic migraine groups, and in the case of episodic migraine, an inability to reduce pain elaboration during an alternative cognitive task emerged as an abnormal behaviour probably predisposing to migraine [5].

A recent cohort population-based study on the long-term effects of migraine on cognitive function showed that cognitive tests in twins with migraine or one of the migraine subtypes did not differ from those of non-migraineurs in any of the tests [6]. This reassuring study should not be considered as conclusive, as illustrated by the editorial [7] which accompanied the article, taking into account that evidence was provided that migraineurs, particularly those with aura, have an increased likelihood of abnormalities in the MRI signal in the cerebellar territory of the posterior circulation and, for women, in the deep white matter [8]. These finding are suggestive of an overlapping of areas involved in aura origin in regions with MRI signal abnormalities, so that many investigators concluded that these signals represent sequelae of ischaemia [9].

In conclusion, the commentary concluded that, in the future, studies will need to account for other categories of migraine and also to perform tests exploring visual-spatial and visual-perceptual organisation and processing [10].

The functions related to visual-spatial performances involve a number of cognitive strategies, and several types of reference frames can be used by the brain to establish relations between our body and the environment. In humans, the parietal and frontal structures involved in "spatial neglect", and a parietal-temporal lobe network, involved in the cortical processing of vestibular information, have also been found to be involved in the egocentric orientation tasks of subjective midline detection and in visual-spatial memory during tasks in which subjects had to mentally remember a path by mental navigation or mental scanning of a map ("topo-kinetic" or "topo-kinesthetic" memory) [11].

It should be noted that dizziness and memory impairment can be induced by many drugs, such as antidepressants, especially TCA, benzodiazepines, muscle relaxants, beta-blockers and anti-convulsant drugs. Also NSAIDs, such as indomethacin, have vertigo as a common side effect, and triptans too can induce central disturbances such as somnolence and dizziness.

It was reasonable to study patients with CTTH and with chronic analgesic overuse who often complain of loss of memory and subjective equilibrium impairment. Because impairment of memory was reported in the past as a proper symptom in chronic headache with and without drug abuse, with a relevant impact on functional disability, we decided to use a topo-kinesthetic memory test, which has been used in the rehabilitation of dizzy patients, to evaluate the ability of patients with chronic headache to perform a complex test using memory as vestibular and proprioceptive capacities [12].

The aim of this test was to establish if the disturbances of equilibrium and memory often complained of by patients with chronic headache were related to the time spent in a standard navigation, and to evaluate a new test aimed at exploring topo-kinesthetic memory in patients with chronic headache with and without medication drug overuse.

Patients and methods

Subjects

During the period 1 January 2004 through 30 June 2004, 36 consecutive patients coming to the Modena Headache Study Center were enrolled: 17 patients suffered from CTTH and 19 from medication overuse headache (MOH) diagnosed following the International Classification of Headache Disorders-2 (ICHD-2) criteria [12]. Moreover, 14 healthy volunteers free from migraine or vestibular disorders underwent the same protocol.

Study design

This was an open, non-controlled, non-randomised trial aimed at recording the responses of patients with chronic headache with and without daily drug use.

Patients were admitted to the Modena University Study Center and enrolled in this study after fulfilling the criteria for the diagnosis of MOH or CTTH by the ICHD-2 [13].

A control group of healthy volunteers matched for sex and age was also tested to obtain a reference parameter with respect to the patients in our experimental setting. In fact, this topo-kinesthetic test has been used only in restricted settings, and widespread accepted reference values have not been established [12].

All human studies were committed and performed in accordance with the ethical standards of the 1964 Declaration of Helsinki. All patients and healthy volunteers gave their informed consent prior to their inclusion in the study.

At baseline, T0, patients were measured for headache and quality-of-life (QoL) parameters. Then, patients with MOH were treated with a standard protocol for these patients aimed at withdrawing the medication overuse by changing the analgesic drug and starting a new prophylactic treatment [14].

Patients with CTTH followed their previous treatment and were retested after one month.

The navigation test was performed in the Audio-Vestibular Center of Modena University.

Navigation test (walking on memorised course test)

The technique is aimed at strengthening spatial analysis and memorising abilities. It is based on the ability to memorise

vestibular and proprioceptive inputs, and to convert them into information regarding the space-time coordinates of the various moves covered [15].

The patient is requested to visually observe and memorise a certain course, painted on a grey carpet with a smooth surface that cannot be perceived by the feet, which can be a simple square, triangle or a circle. The patient walks along the course the first time with closed eyes, then he repeats the exercise two times with open eyes and tries again with closed eyes. The exercise is performed in one direction. Patients performed the exercise barefoot. The time needed to complete the test was recorded for every exercise.

The technique involves many central cortical functions. During step 1 (closed eyes) the patients rely exclusively on the cortex's spatial memorising abilities. In the following steps with open eyes, the patients gain more sensorial inputs, and in the last test we explore the rapid learning for navigational strategy.

Patient evaluation

Patients were administered the Zung Anxiety and Depression scales, a QoL questionnaire and a test to evaluate the overall pain influence on performances as described by Von Korff, the Headache Severity Score [16].

Headache severity

Headache severity (HS) can be described according to Von Korff [14] with the following six HS grades: Grade 0, free of headaches for 6 months; Grade 1, low interference, low intensity; Grade 2A, low interference, high intensity; Grade 2B, medium interference, high intensity; Grade 3, high interference, moderately limiting; Grade 4, high interference, severely limiting.

Quality of life

In 1998 Jhingran developed a 16-item Migraine-Specific Quality-of-Life Questionnaire (MSQ) (Version 2.0) to assess the effect of migraine and its treatment on patients' health-related quality of life (HR-QOL). The MSQ was hypothesised to measure 3 meaningful dimensions: (i) Role Function-Restrictive; (ii) Role Function-Preventive; and (iii) Emotional Function. Results supported the existence of 3 distinct factors that agreed strongly with the hypothesised dimensions [17]. The analysis of post-treatment data suggested that the underlying factor structure of the MSQ varies as a result of treatment. In this study we used this questionnaire.

Statistical analysis

Appropriate statistical analyses were carried out both for intra-group evaluation (paired *t*-test) and for group comparisons (ANOVA, *t*-test and Wilcoxon test).

Results

The demographic data of the patients and the healthy volunteers did not show significant differences between groups and controls with respect to age and sex, as reported in Table 1.

The clinical characteristics of headaches are reported in Table 2, and are grouped as HS, as explained above, medication overuse, number of analgesics taken every observed day and the Headache Index (HI), indicating the number of days with headache in an observed period. The data referring to the values of HS, HI and Medication Overuse were recorded at time T0 and after one month.

The psychological status and the self-evaluation of QoL were recorded for the patients at time T0 and after one month (T1). The values of Zung's scales for anxiety and depression and the results of the QoL test are summarised in Table 3.

To outline all possible alterations in learning and performing the scheduled navigation test, we submitted the patients and volunteers to all the geometric figures at time T0 and T1. In Table 4 the times needed to navigate the triangle both with open eyes and with closed eyes in the first and second test are reported.

In Tables 5 and 6 the times spent to navigate the circle and square, respectively, both with open and closed eyes in the first and second test are reported.

Finally, in Table 7 the performances obtained in the triangle with open and closed eyes at T0, i.e., during the maximum drug use period, in MOH patients divided with regard to the overused drugs (grouped by pharmacological classes) are reported.

Table 1 Demographic data. Data are mean±SD unless otherwise indicated

	Controls	MOH	CTTH
Sex, *n*			
M	4	3	4
F	10	16	13
Age, years	50.8±15.16	56.5±10.35	51.8±17.99

Table 2 Evaluation of headache characteristics. Data are mean±SD

	TEST	MOH	CTTH
Time (T0)	HS	4.7±0.99	4.2±1.52
	MO	3.3±2.65	0,02±0.01
	HI	0.87±0.21	0.9±0.45
Time (T1)	HS	4.3±1.37	3.8±1.22
	MO	1.1±2.23*	0.01±0.01
	HI	0.72±0.35	0.8±0.73

HS, Headache Severity; *MO*, medication overuse (number of analgesic medications/observed days); *HI*, Headache Index (number of headache days/observed days)
*$p<0.01$, T1 *vs*. T0 (*t*-paired test)

Table 3 Patients' status evaluation. Data are mean±SD

	Zung A		Zung D		MSQ	
	T0	T1	T0	T1	T0	T1
Controls	30.8±6.85*	29.7±7.21*	29.6±6.33*	27.8±6.85*	15.57±3.62*	16.32±4.3*
MOH	47.3±9.58	45.7±10.08	46.4±11.47	44.6±9.48	51.8±11.62	46.4±14.80
CTTH	44.5±6.98	45.1±7.12	47.2±8.42	47.5±9.35	46±8.34	45.9±5.78

*$p<0.05$ *vs*. all patient's values (*t*-test)
There were no differences between the T0 and T1 tests for both groups of patients, or between MOH and CTTH

Table 4 Navigation test: triangle. Data are mean±SD

	Closed eyes 1	Closed eyes 2	Open eyes
Controls	14.3±4.97	11.8±4.62	7.5±2.33
MOH T0	27.9±10.12*§	21.1±10.12	10.1±2.95
MOH T1	20.4±8.01*	15.9±5.66°	8.8±2.73°
CTTH T0	34.3±15.38§	23.4±9.54	11.4±3.21
CTTH T1	34.1±13.63§	21.6±8.86	11.1±2.89

ANOVA and Wilcoxon test $p<0.05$ *vs*. controls out of (°)
**t*-test $p<0.002$ (T0 *vs*. T1)
§*t*-test $p<0.05$ (test 1 *vs*. test 2)

Table 5 Navigation test: circle. Data are mean±SD

	Closed eyes 1	Closed eyes 2	Open eyes
Controls	14.7±4.71	10.6±3.19	7.2±1.97
MOH T0	30.3±11.41*§	20.0±6.74	10.0±2.91
MOH T1	20.5±10.57*°	15.6±6.29°	8.8±2.67°
CTTH T0	27.1±11.19§	20.8±10.23	12.4±5.27
CTTH T1	24.7±12.90	20.5±7.85	11.9±4.60

ANOVA and Wilcoxon test $p<0.05$ *vs*. controls out of (°)
**t*-test, $p<0.002$ (T0 *vs*. T1)
§*t*-test, $p<0.05$ (test 1 *vs*. test 2)

Table 6 Navigation test: square. Data are mean±SD

	Closed eyes 1	Closed eyes 2	Open eyes
Controls	18.7±4.19	15.5±4.68	10.0±2.78
MOH T0	38.1±10.76*§	28.3±9.49*	13.2±4.06°
MOH T1	27.9±10.20	22.3±9.34°	12.3±4.38°
CTTH T0	36.4±13.26	28.2±12.11	15.8±5.27
CTTH T1	36.5±13.83	29.4±12.60	16.0±4.96

ANOVA and Wilcoxon test $p<0.05$ *vs*. controls out of (°)
**t*-test $p<0.002$ (T0 *vs*. T1)
§*t*-test $p<0.05$ (test 1 *vs*. test 2)

Table 7 Performances in navigation test (triangle) grouped for overused drugs. Data are mean±SD unless otherwise indicated

Drug	*n*	Open eyes	Closed eyes 1
NSAIDs	6	10.5±2.95	29.2±7.49*
Triptans	5	8.1±2.34	22.4±4.13
Mixtures#	8	10.4±3.13	23.8±12.56*
Controls	12	7.5±2.33	14.3±4.97

#NSAIDs plus caffeine and almobarbital or chlorpromazine
ANOVA for all groups p=0.005
p<0.05 (t-test) *vs*. controls

Discussion

The population data confirm that the three groups were comparable for age and sex.

It is difficult to assess the clinical features of migraine and state objective and measurable parameters to fulfil the classification criteria because migraine ranges in severity, with mild headache and no disability on one extreme to excruciating pain and complete disability on the other. Because of this spectrum of severity, diagnosis alone does not provide enough information to permit the selection of optimal therapy. A headache grading system might help headache sufferers and clinicians match the therapy not only to the diagnosis but also to the overall severity of illness; such a system provides the best hope for cost-effective health care interventions [18]. Therefore, a measurable test could improve the capacity of grading the severity scores of headache patients and aid in improving and monitoring therapeutic strategies.

At time T0 the HS scores were similar in both CTTH and MOH patients, and even if the HS was slightly reduced in MOH patients, this difference did not reach statistical significance.

After one month, analgesic use was significantly reduced in the MOH group, whereas this aspect did not modify the overall evaluation recorded by the HS score. This aspect is reasonable because the overall evaluation of the HS implies a larger time period.

The anxiety and depression scales were significantly higher compared with normal subjects, but did not differ between the two patient groups at time T0 or after one month.

Similar data were reported by the QoL MSQ scale. It was noticeable that QoL started to improve for MOH patients reducing drug overuse but, probably due to the short follow-up and the small sample, there were no significant differences in the total QoL analysis.

The final evaluation of the QoL score was identical in MOH and CTTH patients. This point is noticeable because it suggests that medication overuse could be a mechanism to reach an acceptable QoL even in the case of daily headache.

In Table 4 the times employed by our patients to perform the navigation test in the triangle shape are reported; considering that we found similar values in the circle and square navigation we will discuss only the triangle navigation data.

The open-eyes tests were significantly different at T0 (p<0.02, t-test) both for MOH and CTTH patients *vs*. controls. One month later, the reduction in drug overuse reduced the time of the navigation, so that MOH patients performed the test in a time not different from the "normal" standard, whereas the difference with CTTH was maintained (p<0.02).

The loss of differences between MOH and controls in the open-eyes test after the drug overuse reduction represents the only parameters that change concomitantly with drug overuse withdrawal. It seems to be related to motor performance: this test does not involve memory processes and the patients need only to pay attention to the walking navigation. In this way we can suppose that the test shows that the reduction of drug overuse seems to increase the capacity to carefully perform motor exercises.

The closed-eyes test is characterised by a reduction in walking time due to the learning in the second test (p<0.01, t-paired, both at T0 and T1). At T0 there were significant differences between controls and patients (p<0.002). After drug reduction both MOH and CTTH patients maintained significant differences compared with controls (p<0.03 and 0.001, respectively). The differences between patient groups were not significant at T0, whereas they reached a significant difference at T1, suggesting an improvement of performances in the MOH group (p<0.01, t-test). This difference was maintained also in the second test at T1.

Tests performed with triangle course (Tables 5 and 6) did not add any further information.

The analysis of the navigation test with respect to the overused drugs did not show significant differences, probably due to the small sample. During the first test with closed eyes at T0 it was interesting to note that both NSAIDs and mixtures impaired the triangle test, while triptans did not. The data seem to suggest that triptans

are the drugs that least impair walking ability and memory. This fact could be surprising when compared with the fact that barbiturates and phenothiazines did not alter the performances significantly more than simple NSAIDs. These data need to be confirmed in larger patient samples.

On the other hand, we are aware that the sample size is insufficient to draw significant or definitive conclusions with respect to single drugs, and the data we showed only suggested the possibility that there are differences due to this variable.

Conclusions

First of all, in this study we observed that MOH patients responded well in reducing drug overuse by following a standard protocol to treat overuser patients [19, 20]. In this series the HI did not change significantly because almost all patients continued to complain of near daily headache. Even though the total number of days with headache was reduced by 17%, the HS test was not able to detect an improvement because of the short observational time. The only data suggesting a clinical improvement was the significant reduction in daily analgesic use, which suggests a reduction in daily HS.

On the other hand, the patients suffering from CTTH were shown to be subjects who tended to lead their own lives in the presence of a near daily headache, with a "tolerable" pain, and they had experienced in the past that drugs were useless to reduce their headache, so they did not use analgesics.

In both groups the QoL did not differ significantly either at T0 or after discontinuation of therapy. This point seems to be interesting in order to discuss the significance of daily drug use that does not fulfil the typical criteria of drug abuse, such as compulsive seeking behaviour and withdrawal syndrome, and could suggest avoiding the classification of these patients as "abusers" or addicts because of their daily analgesic use.

Also, the self-evaluation tests for anxiety and depression were similar in both groups and the drug reduction did not change this parameter. Even this evaluation was limited by the brevity of the follow-up period.

The QoL of overusers slightly improved after one month, but without reaching statistical significance (p=0.32, t-test), suggesting that these patients feel little difference even if they reduce drug intake. In this setting analgesic drug use should be considered as only one of the elements in patients suffering from MOH.

Both groups showed an impressive delay in navigating the figures, with little or no differences with regard to the shape (triangle, circle or square).

Navigation with closed eyes was performed in a time that was double that of normal subjects and the second probe with closed eyes at T0 reduced the navigation times proportionally as in controls (ANOVA=NS, 1 *vs*. 2). This observation suggests that patients learn like controls, but were slower to navigate the figures. In fact, in the open-eyes test the differences between patients and controls were significant at T0.

This data could suggest that drug overuse can reduce navigation speed, so that the attention to navigate with open eyes seems to be restored after analgesic overuse reduction and the slight improvement in clinical status leads these patients to normal performances. Otherwise, the CTTH performances did not differ significantly from MOH patients, confirming the stable condition of these patients. We have to consider that these results need to be confirmed with larger series to establish the significance of these differences.

In conclusion, these data suggest that this navigation test seems to be well related to the HI and the HS in patients suffering from chronic headaches. The test seems more strictly related to the QoL and the pain of patients than their drug use. This point is really interesting because doctors and patients often attribute the loss or impairment of memory to drug use. The test examines the topo-kinetic memory and the ability to memorise and actuate a spatial activity that implies the use of visual and vestibular-spatial memory and muscle activity.

These results suggest that this test could be useful to study patients with a mild loss of operational memory or complying difficulties in practical activities.

These data need to be validated in larger clinical settings.

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