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1 Introduction

Headache is a really widespread disease, and it is one of the most common reasons of medical admissions (7). Since there are several different kinds of headaches, it is essential to systematize them in order to find the right therapy, gain scientific knowledge and carry out epidemiological studies in this field. The International Headache Society established their criteria in 1988 and later in 2004 according to which two basic – primary or idiopathic and secondary or symptomatic – types of headaches can be distinguished. Main forms of primary headaches are migraine, tension and cluster headaches. Migraine typically affects young and middle aged women and produces unpredictable attacks. It is often accompanied by severe symptoms, harms people’s quality of life, and it has serious economical consequences (8). Although the existence of several predispositions, precipitating ad protective factors has been confirmed, the exact etiopathogenesis and patomechanism of migraine is still not known (3, 5). The most important precipitating factor is stress, the constant form of which leads to the progression of migraine (6). Treatment of this disease is extremely complicated; pharmacotherapy is accompanied by several unwanted side-affects (5). Migraine patients often overdose painkillers and become addicted to them, at the same time they often suffer from chronic headaches (7). Although migraine includes acute episodes and periods with no symptoms, it also has a chronic affect on patients (8). It has a long-term harmful affect on their mental state, relationships, social life, carrier and their whole life (7, 8). Although e more there is and more effective medication at our disposal for preventing and soothing migraine attacks, even nowadays it is often the case, that by traditional biomedical way of thinking and somatic medicine full recovery or significant improvement of migraine cannot be reached (5). Partly for this reason, in the last few decades there has been a growing demand for relaxation techniques creating psychophysiological harmony. These techniques are regularly used especially in prevention and in the therapy of psycho-vegetative and anxiety disorders (2). Since they have been effective in clinical practice (1, 2), and combined with traditional medical treatment and other psychotherapies they make therapy more effective, they have gained a central position in medicine (4).
2 Objectives

This research focused on the effect of Schultz’s autogenic training combined with confirmation trainings and motion therapy elements on primary headaches, especially on spontaneous and nitro-glycerine-provoked headache. The aim of this research was to find answers to the following questions:

1) Is autogenic training combined with confirmation training and motion therapy elements effective for treating primary headaches?
2) Is there a difference in effectiveness in the case of various types of primary headaches?
3) How does the effect of autogenic training develop in time, during the periods of learning and practising?
4) Does combined autogenic training have an affect on medication applied for treating primary headaches and the use of anxiolytic drugs?
5) Does combined autogenic training have a justifiable therapeutic affect on immediate/transitory and delayed migraine provoked by nitro-glycerine?
6) Is there a significant difference in the plasma cortisol levels between controls and migraine patients without aura before nitro-glycerine ingestion? Is there a significant difference in the plasma cortisol levels between patients practising autogenic training and non-AT patients before nitro-glycerine ingestion?
7) What kind of changes can be found during nitro-glycerine provocation? Is there a significant difference between:
   • controls and migraine patients without aura,
   • patients practising autogenic training and non-AT patients,
   • and patients developing and not developing a migraine attack?
8) Do changes in blood pressure and pulse frequency levels – caused by nitro-glycerine provocation – differ according to
   • diagnosis (controls or migraine patients without aura),
   • practising autogenic training (AT patients and non-AT patients),
   • development of provoked headaches (patients with or without immediate / transitory or delayed migraine)

statistical analysis was carried out for the above-mentioned subject groups?
3 Method

In order to find answers to the questions above, we carried out two independent studies involving female migraine patients and controls in their reproductive years.

3.1 Subjects

In our first study patients suffering from migraine, tension and mixed headache, in our second study migraine patients and healthy controls were selected. Patients were being treated at the Headache Clinics of National Institute for Sports Medicine and National Institute of Psychiatry and Neurology. Controls were selected from hospital staff and students. A detailed medical history was taken from each subject, concerning especially headaches and other mental or neurological disorders. Before selecting for the studies they underwent complete physiological, neurological and psychological examinations, as well as laboratory tests. For diagnosing headache the International Headache Society 1988 (for the first study) and 2004 (for the second study) criteria were used. Subject compliance was checked verbally at control visits and consultations. Apart from this, subjects kept a headache diary on a daily basis, which was also checked. Only subjects who practised every day for a period of 4 months (first study) and a period of 6 months (second study) were selected. In the second study only those subjects were selected who took no medication on the day of the examination, up to the time of the last blood test.

In the first study data of migraine patients were compared to data of patients suffering from tension and mixed headache. In the second study data of migraine patients and healthy controls were compared. Besides this, in the first study the observation period data of each headache group were compared to data obtained while learning autogenic training. The Ethics Committee of National Institute of Psychiatry and Neurology approved the study protocols. Having read the information booklet about the study, every subject was asked to give a written consent before starting examinations.

3.2 Measured parameters

- a headache diary in order to keep track of the frequency and the nature of headaches and the effectiveness of applied therapies,
- headache intensity scored on a verbal scale that measured from 0 to 10,
- a follow-up of the quality of headache and the effect of autogenous training in the migraine provocation, measured by previously set questionnaires,
• records of blood pressure and pulse frequency at baseline and every hour thereafter with the use of an OMRON MX3 digital blood pressure monitor,

• state/trait anxiety and mood disturbances measured by Spielberger’s State-Trait Anxiety Inventory and Zung Self-Rating Depression Scale,

• four blood tests carried out with the use of the Vacutainer system® (Becton Dickinson) Baseline blood sample was drawn at 7:00 a.m., the second sample after the administration of nitro-glycerine at 9:00 a.m., the third and the fourth samples 60 and 120 minutes after the beginning of the migraine attack (mean 310 minutes and 370 minutes after nitro-glycerine.). In subjects with no migraine attack third blood sample was taken 5 hours and fourth blood sample was taken 6 hours after ingesting nitro-glycerine,

• plasma cortisol concentrations measured directly by RIA method without previous extraction, with the use of kit commonly available.

3.3 Statistical analyses

3.3.1 First study: The effect of combined autogenic training on treating primary headaches

Means obtained during the second, third and fourth month of the observation period were treated as basic data in the study of the effectiveness of autogenic training. One-way and bivariate ANOVA were used for the statistical analyses of the mean values gained from different patient groups, which were accompanied by post hoc comparisons. Temporal changes of parameters were analysed by repeated measures of ANOVA. Correlations were established by Spearman rank correlation test.

3.3.2 Second study: The effect of combined autogenic training on provoked-provoked headaches

Data obtained were analysed by one-way and bivariate analyses of variance (ANOVA, MANOVA) Non-parametric results were analysed by Friedman’s ANOVA and Mann-Whitney’s u-test. Pearson’s $\chi^2$ test was applied to find out if there is a difference in the development of headache amongst the different patient groups. Spearman’s rank correlation test and Pearson’s product moment correlation test were used for establishing correlations. A confidence interval of 95% was calculated by standard methods.
4 Results

4.1 First study: The effect of combined autogenic training on treating primary headaches

- Headache frequency was the highest amongst tension headache patients in the fourth month of the observation period before the start of autogenic training. This parameter was the lowest in the migraine group. Patients suffering from tension and mixed headaches took almost 2.5 times as much anxiolytic drugs as migraine patients. Patients with mixed headaches took a larger amount of anti-migraine drugs than migraine sufferers, and patients with tension headache took none of these drugs at all.

- During observation period there was no significant change in headache frequency and the use of painkillers, anti-migraine and anxiolytic drugs.

- Regarding data obtained from all the patients, after four months of autogenic training, a significant decrease can be seen in headache frequency, the use of painkillers, anti-migraine medication (triptanes and ergot-derivatives) and anxiolytic drugs. Decrease of the amount of anxiolytic drugs differed significantly in the three patient groups.

- Headache frequency decreased significantly in the tension and mixed headache group, as soon as the first month of autogenic training. Decrease was slower and milder in the migraine group and a significant change took place only in the third month of autogenic training. Decrease of the anxiolytic drugs was fastest and strongest in the tension group once again. The use of anti-migraine medication and painkillers decreased in a similar way.

- In the analysis of data obtained during the autogenic training period, significant correlations were found between changes of headache frequency and the use of painkillers. In contrast, there was no significant correlation between changes of headache frequency and changes in the use of anxiolytic medication.

- There was no significant difference between parameters (age, headache frequency) of dropout patients and of patients who completed autogenic training. Most patients dropped out from the migraine group; dropout rate was almost the same in tension and mixed headache groups. Most patients dropped out in the fifth month, on the first week of the learning period, blaming mainly lack of time.
4.2 Second study: The effect of combined autogenic training on provoked-provoked headaches

- Nitro-glycerine provoked headache in a group of subjects. There are two different kinds of headaches. Immediate/transitory headache is milder, it doesn’t fulfil the criteria of migraine without aura and it disappears spontaneously within an hour. A migraine attack typically develops an average of 250 minutes after administering nitro-glycerine, it fulfils the criteria of migraine without aura and treatment with medium or strong painkillers was necessary.

- A significant difference was found in the scores of immediate/transitory headache between controls and migraine patients. There was, however, a significant difference in headache scores of migraine patients taken at two different times of testing during migraine attack.

- There was no significant difference between subjects practising autogenic training and non-AT subjects in the frequency of immediate headaches and migraine attacks, neither in the scores of these headaches.

- There was no relationship found between immediate headache and development of migraine attack.

- There was no significant correlation between baseline plasma cortisol concentration and psychometric scores, but a significant negative correlation was found between baseline plasma cortisol concentration and the intensity of migraine attack.

- There was a significant increase in plasma cortisol concentration during the migraine attack. A strong correlation was found between changes of plasma cortisol concentration and changes of migraine headache scores. There was no significant difference between the groups formed on basis of diagnosis and autogenic training practice.

- One hour after ingesting provoked, blood pressure and pulse frequency decreased significantly. There was no significant difference as regards to this decrease between migraine and control groups or between subjects with or without provoked migraine attacks. A significant difference was found between subject practising autogenic training and non-AT subjects. Blood pressure and pulse frequency was significantly more stable in subject practising autogenic training.
5 Summary

In my research I studied the effect of Schultz’s autogenic training combined with organ formula and motion therapy elements on primary headaches, especially focusing on spontaneous and nitroglycerine-provoked headache. My aim was to establish whether frequent AT practice influences spontaneous headaches e.g. migraine attacks and use of medications in the treatment of migraine, provoked migraine, as well as changes in plasma cortisol levels, blood pressure and pulse frequency during migraine provocation.

In our studies we established a 4-month observation period, and patients learned and practiced autogenic training in the next four months. We compared the effects of autogenic training on measured parameters and during nitroglycerin provocation to a control group. During the regular, 4-month practice of autogenic training the frequency of headaches and the use of medications decreased as compared to data during the observation period in all headache groups (migraine, tension and mixed headache). Effect of autogenic training appeared earliest and was most pronounced in tension and mixed headache groups, while in the migraine group a significant decrease was found only from the third month of autogenic training practice. While the decrease in headache frequency was strongly associated with the decrease in use of painkillers and antimigraine medications, there was no significant association found in case of the use of anxiolytic drugs.

NO donor nitroglycerine-provoked headache is one of the most widely used human migraine models. In our research we aimed at establishing whether frequent practice of autogenic training and its concomitant application during nitroglycerine treatment is able to influence the migraine provoking effect of the NO donor molecule and the increase of plasma cortisol levels. Our results indicate that nitroglycerine generates migraine attacks in migraine patients which in addition is accompanied by an increase in cortisol concentration. This migraine headache develops on average five hours after nitroglycerine ingestion and it can be clearly distinguished from the transitory headache appearing shortly after nitroglycerine ingestion and lasting about 30-60 minutes. Autogenic training significantly decreased the effect of nitroglycerine on blood pressure and pulse frequency. Despite of these, our results indicate that frequent autogenic training practice influenced parameters of neither immediate/transitory, nor migraine headache and had no influence on the increase of plasma cortisol levels either. These latter can be extinguished only by triptans used as medication for migraine attacks.
Our results indicate that autogenic training is an effective therapy in case of all three patient groups investigated, decreasing both headache frequency and related use of medications. Despite of these, it is unable to significantly influence migraine headache provoked by a strong chemical stimulus (e.g., a NO donor). Therefore autogenic training has a favourable effect on the quality of life of migraine patients, however, drug therapy is indispensable for treating evolving migraine attacks.
6 References

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8 Publications

8.1 The dissertation is based on the following journal articles and citable abstracts

8.1.1 Journal articles

1. G Juhasz, T Zsombok, X Gonda, N Nagyne, E Modosne, G Bagdy
   Effects of Autogenic Training On Nitroglycerin-induced Headaches
   Headache 47:1-13; 2007

2. Zsombók Terézia, Juhász Gabriella, Gonda Xénia, Vitrai József, Bagdy György:
   Kognitív- és szimbólumterápiás elemekkel módosított autogén tréning hatása az
   elsődleges fejfájós betegek kezelésére
   Psychiatria Hungarica, 2005.20.1. p.25-34

   A nitroglicerin által okozott fejfájások

   Effect of autogenic training on drug consumption in patients with primary headache:
   An 8-month follow-up study
   Headache 43 (3): 251-257 MAR 2003

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8.1.2 Citable abstracts and authors replay

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   A fejfájás oldása relaxációval.
   Programfüzet: 2. oldal.

   A migrénes roham rizikófaktorai a nitroglicerin indukálta humán migrénmodell
   alapján.
   A szerotonin szerepe a migrén kialakulásában.

   Az autogén tréning hatása az elsődleges fejfájós betegek kezelésére: nyolc hónapos követéses vizsgálat

   Aura nélküli migrénes betegek genetikai vizsgálata a szerotonnerg rendszerben mérhető
   neurokémiai eltérések tükrében. Kezdeti eredmények.
   Előadás.
   Cephalalgia Hungarica, 2002. no.9: Pótlap.

   Az 5-HT2A-receptor-gén és az 5-HT transzporter gép polymorfizmusának vizsgálata
   migrénben. A Magyar Klinikai Neurogenetikai Társaság IV. Symposiuma nemzetközi

7. **Zsombók T.,** Berghammer R., Vítrai J.
   A depresszív szindróma kimutatása háromféle krónikus fejfájós betegcsoportban és
   összefüggésének felmérése az életminőséggel migrénes és tenziós fejfájós betegeknél.

   Komorbiditásról, személyiségjellemzőkról különböző típusú fejfájós páciensek
   Balatonalmádi.

9. **Bagdy, G., Zsombok, T.,** Gonda, X., and Juhasz, G.: 
   Autogenic training might help headache patients.
8.2 Other publications, oral and poster presentations

8.2.1 Publications

1. Gonda X., Rihmer Z., Juhasz G., Zsombók T., Bagdy G
   High anxiety and migraine are associated with the s allele of the 5HTTLPR gene polymorphism

   The 5HTTLPR polymorphism of the serotonin transporter gene is associated with affective temperaments as measured by TEMPS-A.

   Sumatriptan causes parallel decrease in plasma calcitonin gene-related peptide (CGRP) concentration and migraine headache during nitroglycerin induced migraine attack
   Cephalalgia 25 (3): 179-183 MAR 2005

   NO-induced migraine attack: strong increase in plasma calcitonin gene-related peptide (CGRP) concentration and negative correlation with platelet serotonin release
   Pain 106 (3): 461-470 DEC 2003

   Despite the general correlation of the serotonin transporter gene regulatory region polymorphism (5-HTTLPR) and platelet serotonin concentration, lower platelet serotonin concentration in migraine patients is independent of the 5-HTTLPR variants
   Neuroscience Letters 350 (1): 56-60 OCT 16 2003

   Association analysis of 5-HTTLPR variants, 5-HT2A receptor gene 102T/C polymorphism and migraine
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7. Bartkó Gy., Békéssy M., Szél K., Zsombók T., Mayláth E.
1985: A gyógyszeres kezeléssel való hiányos együttműködés okainak vizsgálata
schizophren betegeknél.

8. Zsombók Terézia
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9. Zsombók Terézia
A migrén okai és kezelési lehetőségei: 1. rész

8.2.2 Book
Berghammer Rita, Zsombók Terézia

8.2.3 Book chapter
Dr. Zsombók Terézia
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Családorvosok kézikönyve, 2006, Biofil könyvek,(Szerk.: Dr. Csalay László)
p 403-410.

8.2.4 Educational film
Zsombók Terézia, Bánhidi Borbála, Tölgyesi Balázs
„Mozgásterápia a krónikus fejfájós betegek kezelésében – 2001”

8.2.5 Oral presentations
1. Zsombók Terézia, Tóth Krisztina
Dohányzás és/vagy az orális fogamzásgátló szerek alkalmazásának gyakorisága
fejfájós nőbetegek körében (egy Fejfájás Ambulancia egy éves adatai alapján).
2. Zsombók T., Koperdák M., Berghammer R., Vitrail J.
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A Magyar Rehabililitációs Társaság III. Vándorgyűlése. „A pszichiátriai rehabilitáció és
Programfüzet 3. oldal.

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Headache in Practice: Good Parkinson and Migraine Practice. Magyar Parkinson
Társaság, a Magyar Fejfájás Társaság Közös Továbbképző Rendezvénye. 2003.

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A krónikus fájdalom konzultatív pszichiátriai vonatkozásai.

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Előadás.
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Ritkán előforduló EEG-jelenség értelmezésének nehézségei krónikus fejfájós
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8. **Zsombók T.**
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**8.2.6 Poster presentations**

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2. Kökönyei Gy., Janicsák, H., **Zsombók, T.**
  Emotional awareness and alexithymia in outpatients of a headache clinic and controls.

  A szorongás és a szerotonin transzporter gén s alléljának összefüggése migrénesekben és egészséges személyekben.

  Migrénes és nem elsődleges fejfájós betegek általános és aktuális szorongásszintjének és hangulatvárának összehasonlító elemzése.

5. Berghammer, R., **Zsombók, T.**, Vitrai J.
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  Krónikus fájdalomban szenvedők gyógyszeres kezelését támogató megbírkozási stratégiák.
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