THE ROLE OF DECISION-MAKING CONSIDERATIONS IN THE TREATMENT OF PRIMARY HEADACHES

Ph.D. Thesis

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1. Introduction. Primary headaches and migraine

Headache is one of the mostly investigated complaints, whereby doctors meet. Headache could be a symptom of severe, life threatening disease, however in most of the cases it is only a benign tension type headache or migraine. The headaches are divided into four major categories by the classification of International Headache Society (IHS 2004). Primary headaches belong to the first group, as the migraine, tension type headache, trigeminal autonomic cephalalgias and other primary, infrequent headaches. Primary headache is estimated to the main group of cephalalgias, because 87% of the headaches are non organic. The group of secondary cephalalgias subsume headache attributed to head and neck trauma, cervical or vascular disorder, non vascular intracranial disorder, substance or its withdrawal, infection, disorder of homeostasis, disorder of cranium, neck, eyes, ears, nose, psychiatric disorder, these entities add up the 10% of all headaches. In the third group comprise the rarer concurrent headaches as cranial neuralgias and central or primary facial pains. According to former studies 47% of the population suffer from recurrent headaches, within this group 10% of the patients have migraine, 38% have tension type headache and 3% of the patients have chronic headaches. We are disposed to believe that headaches are simply, not too severe diseases, nevertheless this does not mean, that headaches are not represent remarkable burden for economy. Under international data (USA, UK) the prevalence of migraine is 12% and 70% of migraine patients need cure during the headache. This doesn't mean generally an outpatient or bed-case management, because the major part of patients can cure the headache self with certain medicaments. However through this time most of the patients are unable to work or learn. When international data are projected to Hungary, migraine results 1.4 million drop-out workdays and 2.8 million workdays with decreased efficacy per a year. According to European Union data, migraine is the most expensive disease from neurological disorders amounts 27 billion Euro per a year, the major part derives from indirect cost means drop-out workdays and workdays with decreased efficacy.

2. Aims of the investigations

In the thesis three different questions were investigated in the theme of primary headaches.

First, we investigated in our own migraine patients, with and without white matter hyperintensities (WMH), migraine history and risk factors were analyzed, which can lead to the development of migraine related white matter hyperintensities.

In the second part the hypothetical association was analyzed between the migraine and magnesium deficiency. Further investigations referred that Mg deficiency plays etiological role in the pathogenesis of migraine. Whereas Mg is mainly intracellular cation, thereby a simple serum Mg measurement not gives us true information about the whole body Mg content. Therefore the total body Mg content was investigated with a per oral Mg load test in the comparison between the group of patients with migraine and healthy volunteers.

In the third part a trigeminal autonomic headache, SUNCT (Short Lasting Unilateral Headache with Nasal Conjunction and Tearing) syndrome was studied. We investigated the periods of our three patients, and we found a new, effective short-term prevention therapy, which can be offered for the treatment of SUNCT.

3. Risk factors of migraine-related white matter hyperintensities

3.1. Migraine and white matter hyperintensities: introduction

Migraine is not as benign a disease as it was thought before the imaging era since migraine is an independent risk factor for deep white matter lesions, silent posterior circulation territory infarcts, and infratentorial hyperintense lesions. Migraine patients have an almost fourfold greater risk to develop white matter lesions than non-migraine controls, and the prevalence of these lesions is higher in migraine with aura than in migraine without aura. The risk of developing white matter lesions is higher in female migraineurs and in patients with higher attack frequency and longer disease duration. Furthermore, it seems that brain white matter lesions do not correlate with age. Brain white matter hyperintensities are frequent, but not specific alterations in the MRI, under its definition small, punctual (3-7 mm) lesions in the perinventricular or in the deep white matter, appear in the T2 and FLAIR sequences of the MRI, but not can be seen in the T1 sequence.

The clinical significance of white matter hyperintensities (WMH) is uncertain and the pathogenesis of these lesions is likely multifactorial. A number of pathophysiological mechanisms have been proposed including attack-related oligemia and focal hypoperfusion, glutamatergic excitotoxicity, immune-based white matter demyelination, and mitochondrial dysfunction. Several studies considered the role of inflammation as a vascular risk for brain white matter lesions in migraine. Elevated C-reactive protein found in migraine patients is a sensitive indicator of active systemic inflammation and a marker of oxidative stress. Increased proinflammatory cytokines (IL-1, IL-6, TNF-a) have been reported during acute migraine attacks, as well as in the interictal periods. Repeated sterile vascular inflammation results in endothelial injury of the cranial blood vessels, cranial arteriopathy, and consequent thrombosis. It has been suggested that cortical spreading depression causes disruption of the blood brain barrier through a matrix metalloproteinase-9-dependent cascade mechanism which may result in local tissue damage. It is also known that endothelial dysfunction associates with an increased rate of cerebrovascular ischemic events, and genetic factors (such as angiotensin converting enzyme insertion/deletion, methylenetetrahydrofolate reductase C677T polymorphisms, and von Willebrand factor activity) which increase the susceptibility of endothelial dysfunction have been linked to migraine.

Although migraineurs, particularly with aura, have a higher cardiovascular risk profile than individuals without migraine, the presence of white matter lesions proved to be independent of a history of hypertension, diabetes, smoking, hypercholesterolemia, hyperhomocysteinemia, patent foramen ovale with right-to-left shunt, and oral contraceptive use. Associations with antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulans) and abnormal coagulation parameters (antithrombin-III, protein S, protein C) were also not found. Because of the high prevalence of white matter hyperintensities, and the partly contradictory and uncertain etiological data, we have investigated the possible risk factors for subclinical brain white matter hyperintensities in our own migraine patients by analyzing their routine clinical data.

3.2. Patients and methods
3.2.1. Subjects and studies

Subjects included in this study were referred to the Outpatient Headache Department of the Department of Neurology, Medical School, University of Pécs, Hungary between 2007 and 2009. All the patients who were chosen for the study met the criteria of migraine patients as defined by the International Headache Society. Further, patients were also selected based

on the lack of major comorbidities, such as hypertension, cardiac disease, diabetes, thyroid gland dysfunction, oncological and haematological diseases, infectious diseases (e.g. HIV, hepatitis), central nervous system demyelination (e.g. multiple sclerosis), and genetically inherited disorders (e.g. CADASIL). Altogether 186 migraine patients were investigated in the study (141 patients without aura, 45 patients with aura, age range 18–58 years, mean age 36.4 years, SD: 8.9; 156 females and 30 males). Based on the findings of brain magnetic resonance imaging (MRI) studies, patients were divided into two groups: patients with WMH (WMH group, n = 58, mean age 40.2 year, 54 patients had supratentorial hyperintensities, 4 patients had cerebellar hyperintensities) and patients without WMH (WMH group, n = 128, mean age 34.9 year).

All participants underwent a structured clinical examination (history taking, physical examination, blood pressure measurement, serum and urine tests, brain MRI study) to identify comorbid medical disorders. Gender, migraine type, disease duration, attack frequency, history of smoking and taking oral contraceptives, serum cholesterol LDL, uric acid, homocysteine levels, and thyroid-stimulating hormone levels with thyroxine and triiodothyronine when necessary were routinely examined. In all cases when aura symptoms and/or WMH were present, patients were tested for vasculitis (antinuclear antibody, antineutrophil cytoplasmic autoantibody, antiphospholipid antibody, lupus anticoagulant), for Lyme disease (serum ELISA screening with Western blot testing), and for patent foramen ovale (transthoracic and transesophageal echocardiography).

3.2.2. MRI protocol

The brain MRI examinations were carried out with an MR scanner operating at 3 T (Siemens Trio Tim, 12 channel head coil). A qualified neuroradiologist who was blinded to migraine diagnosis and clinical data rated the WMH. WMH were considered if visible as hyperintense on T2- weighted and FLAIR images, without hypointensity on T1- weighted scans, and were larger than 3 mm.

3.2.3. Statistical analysis

Statistical analysis was performed using the SPSS 15.0 statistical package (SPSS Inc., Chicago, IL, USA). Chi-square, Fisher's exact test, non-parametric Mann–Whitney and finally a binary logistic regression was performed to predict the presence of WMH from a set of independent variables.

3.3. Results

1. There was no statistical difference between females (n=48 out of 156, 30.7%) and males (n=10 out of 30, 33.3%), as well as between migraine patients without aura (n=42 out of 141,

30.5%) and patients with aura (n=16 out of 45, 35.6%) in relation to the presence of WMH (Table 1).

Table 1. Patients

WMH+patients	n	percentege of patients
women	48/156	30.7%
men	10/30	30.33%
migraine without aura	42/141	30.5%
migraine with aura	16/45	35.6%

2. The number of patients with WMH increased with the increase of disease duration, in patients with above 20 migraine years hyperintensities were significantly more frequent than in those with less than 20 years of duration (under 20 years n=28/120, 23.3%, above 20 years in n=30/66, 45.6%, p=0.007). When examining the association between the disease duration and the presence of WMH according to migraine type, it was found that both migraine patients without and with aura have a longer disease duration with WMH, than patients without WMH (Table 2).

Table 2. Differences between the WMH- and WMH+ groups in relation to disease duration and attack frequency in migraine patients without and with aura

		Patient number	Disease duration	p-value	Attack frequency	p-value
			[years]		[attack/month]	
All patients	WMH-	128	14.3±8.5	0.004	4.1±3.0	0.017
	WMH+	58	19.9±11.6		5.5±3.6	
Patients without aura	WMH-	99	14.7±8.7	0.3	4.6±3.1	0.017
	WMH+	42	19.7±11.7		6.2±3.6	
Patients with aura	WMH-	29	13.1±7.9	0.047	2.4±2.4	0.067
	WMH+	16	20.3±11.8		3.5±3.0	

WMH- patients without white matter hyperintensities, WMH+ patients with white matter hyperintensities. The diseases duration and attack frequency values are presented in mean ± 1 SD.
p values are based on Mann–Whitney statistical analysis

3. Although the proportion of migraine patients with WMH increased with the monthly migraine attack frequency (0–1 attack/month: n=7/37, 18.9%, 2–7 attacks/month: n=36/114, 31.5%, C8 attacks/month: n=15/35, 42.9%), there was only a trend towards statistical significance (p=0.08) when the patients were examined in three groups according to their attack frequency. Conversely, when the attack frequency of the WMH+ group was compared to the attack frequency of the WMH- group, a significantly higher attack number was found in the WMH+ group (Table 2). When examining the effect of attack frequency on the presence of brain WMH in migraine subgroups, it was found that migraine patients without aura and with WMH have a higher attack frequency than patients without aura and without WMH

(Table 1). In patients with aura the same tendency was seen, but the difference was not statistically significant (Table 2).

4. WMH did not occur more frequently in smokers (n=18/52, 34.6%) than in non-smokers (n=40/134, 29.8%), but smoking was significantly associated (p=0.001) with increased monthly attack frequency (\5 attacks/month: n=87/134, 64.9% in non-smokers, n=47/134, 35.0% in smokers, C5 attacks/month: n=20/52, 38.4% in non-smokers, n=32/52, 61.5% in smokers).

5. There was a significant relation between abnormally high serum homocysteine levels and the incidence of brain WMH; out of 60 patients tested for serum homocysteine 9 had WMH and homocysteine levels were elevated in all 9 patients (p=0.009).

6. Subclinical hypo- (n=8) and hyperthyroidism (n=6) was detected in 14 patients (14/186= 7.5%). Out of these patients, eight had WMH (4 patients in both groups, 8/14=57.1%). Statistical analysis showed the subclinical thyroid dysfunction occurred significantly more frequently in the WMH+ group than in the WMH- group (p=0.038).

7. Although the statistical analysis did not show an increased risk of WMH in migraineurs with high cholesterol, LDL cholesterol (p=0.06) and high uric acid levels (p=0.07), the cholesterol, LDL cholesterol and uric acid values were found more frequently in the elevated range in the WMH+ group (n=18/41, 43.9% for cholesterol, LDL cholesterol, n=7/15, 46.6% for uric acid) than in the WMH- group (n=40/145, 27.5% for cholesterol, LDL cholesterol, n=51/171, 29.8% for uric acid).

8. When the effects of all the predictor variables were examined, only two good predictor variables were found: the disease duration (p<0.01) and the attack frequency (p<0.05) (Table 3). There was no significant effect with all the other variables (p>0.1) (Table 3)

Table 3. Results of binary logistic regression for white matter hyperintensities

| | Examined variables | p-value | OR | 95% CI or OR | |
				lower	upper
Step 1	Disease duration	0.090	1.046	0.993	1.103
	Attack frequency	0.018	1.164	1.026	1.321
	Age	0.913	0.997	0.947	1.049
	Gender	0.865	1.087	0.414	2.855
	Smoking	0.249	0.584	0.234	1.457
	Thyroid function	0.289	0.637	0.277	1.465
	Cholesterol	0.135	0.498	0.200	1.242
	Uric acid	0.447	0.515	0.093	2.849
Step 7	Disease duration	0.005	1.051	1.015	1.089
	Attack frequency	0.017	1.153	1.026	1.295

The table presents the p value, the odds ratio (OR) and the 95% confidence interval (CI) for the OR for all of the variables at Step 1 and for the variables that were significant at Step 7 of the backward stepwise elimination procedure

9. An elevated antiphospholipid antibody titer was only found in one patient. Echocardiography showed a tiny patent foramen ovale with right to left shunt in two migraine patients with aura and with brain WMH. There was no patient with pathologic Lyme serology.

3.4. Discussion

In this study, we have investigated possible risk factors for brain WMH based in migraine history and blood tests. To get more accurate data on those factors which may influence the formation of WMH, diseases which can associate with the presence of brain WMH without migraine, including hypertension, were excluded from our study. We found significantly higher hyperintensity incidence in patients with longer migraine duration, higher headache frequency, subclinical hyper- and hypothyroidism, and elevated plasma concentrations of homocysteine, while in the cases of cholesterol and uric acid, there was a trend towards statistical significance. Statistical difference was not found between migraine patients without and with aura in relation to the presence of WMH, but most of the patients in the WMH+ group had only supratentorial signal abnormalities. There are differences between our results and the previously documented ones, and we suppose that these are based on the limitations of the performed studies due to differences in patient selection and sample size. The relation between disease duration and attack frequency to the WMH is not surprising if we take into account the pathophysiology of migraine. During the attack several intracranial pathologic processes are detectable, including intracerebral haemodynamic changes, local inflammatory responses, excessive neuronal activation and excitotoxicity, which may all lead to tissue damage. Although there are regional differences and predilection sites for tissue damage, basically, the migraine attack affects the whole brain. It is known that there are differences among migraine patients in relation to the risk of the WMH. The risk depends not only on the disease duration and frequency, but the migraine type, attack duration, and comorbid conditions can also influence it. The comorbid conditions are mainly routine stroke risk factors and these may lead to tissue damage by direct (e.g. blood vessel endothelium dysfunction, hypercoagulation, embolization) or indirect (e.g. smoking) effects. In our study, the occurrence of WMH was not higher in smokers than in non-smokers, but smoking increased the headache frequency, therefore smoking may indirectly cause white matter hyperintensities. These data are consistent with the previously reported ones showing higher prevalence rates for headache amongst smokers compared to non-smokers.

Plasma homocysteine concentration is controlled by genetic (MTHFR C677T mutation), nutritional(vitamins, folate, B6, B12) and acquired (smoking, alcohol consumption, renal diseases, malignancies, inflammation, daily physical activity) factors. It has been found that migraine patients with aura who are homozygotes for methylene-tetrahydrofolate reductase (MTHFR) C677T variant, are at risk for elevated levels of homocysteine, and homocysteine-related endothelial dysfunction may be involved in the initiation and maintenance of migraine.

Although subclinical thyroid gland dysfunction was found in few patients in our study, more than half of these patients had brain WMH. Subclinical thyroid gland dysfunction can be a risk factor for WMH in migraine, but currently there is no definite evidence to confirm this. Hyperthyroidism can associate with atrial fibrillation and cardioembolic stroke and may lead to a hypercoagulability state. Hypothyroidism is associated with a worse cardiovascular risk factor profile including elevated cholesterol and lowdensity lipoprotein levels, diastolic hypertension, increased homocysteine and C-reactive protein concentrations, impaired thyroid hormone action on target tissue by smoking, tendency toward decreased fibrinolytic activity in mild and moderate hypothyroidism, and endothelial dysfunction with progression to atherosclerosis.

We found WMH more frequently in our migraine patients with elevated serum cholesterol and uric acid levels, and we speculate that if there is a relation between migraine and cholesterol and uric acids levels, this can be based on altered endothelial dysfunction and migraine attack frequency. The presence of hypercholesterolemia and dyslipidemia in patients with migraine may increase the risk of vascular wall injury. Hypercholesterolemia is associated with an increase in endothelial permeability, the retention of lipoproteins within the intima of blood vessels, inflammatory cell recruitment and foam cell formation filled with oxidative-LDLs, and finally these processes progress to atherosclerotic plaque maturation. Cholesterol crystals, a component of human atherosclerotic plaques, could also cause an inflammatory response and neuronal injury in the brain with persistent activation of microglia and astrocytes via microembolization. Furthermore, a number of epidemiologic data show that an elevated serum uric acid level is a powerful predictor of an increased risk of a cardiovascular event including stroke and silent brain infarcts, however, the available data are contradictory. It is entirely plausible that chronic elevations in serum uric acid levels have harmful effects on platelet, smooth muscle, and endothelial function, but the neuroprotective, antioxidant effect of high uric acid levels may associate with improved outcome in the peri-ictal period. In conclusion, this study provides additional data on the etiology of migraine-

related WMH supporting the former assumptions that a wide range of factors contribute to lesion formation. These include attack-related intracerebral changes and direct or indirect effects of comorbid diseases.

Development in understanding the pathophysiology of migraine and the pathology of WMH, the use of effective therapy for migraine attack and prophylaxis, detection and treatment of vascular risk factors, and avoiding smoking may help to prevent the development of the hyperintensities.

4. Oral Magnesium load test in patients with migraine

4.1. Introduction

Magnesium is an essential intracellular cation in the body, the fourth mostly occurring mineral agent, and it is involved in numerous physiological processes. Magnesium is a cofactor of more than 300 physiological processes, it plays a role in the synthesis of DNA, RNA, protein, in the production of energy (ATP-Mg complex), and stabilize the membrane of the mitochondria. Magnesium has in important function in the metabolism of bones. Mg counts as a natural Ca antagonist, because it is able to activate the Na-K-ATP-ase, able to inhibit the influx of Ca into the cell. Mg participates in action of neuromuscular junction (inhibit the excretion of Ach in the nerve terminal, stabilize the sarcolemma), in muscle and cardiac cell contraction, in balancing of blood pressure, in the metabolism of glucose and insulin.

The Mg content of the adult human is approximately 25 g, 60% of the total amount is in the bones, 40% is in the muscle cells or other soft tissues, and less than 1% of the total body Mg is present in the blood. Mg mainly an intracellular cation, the main store is the bone, in case of Mg deficiency it could be evolved from the bones, but it is a time-consuming procedure, it takes a few weeks. Therefore the Mg deficiency cannot be equalized fast, accordingly the serum Mg level cannot reflect the correct Mg content of the body. The shift between the intra- and extracellular part is a slow process; it is controlled by the electrochemical gradient, but there is also known an ATP dependent Na-Mg changer ion pump. Therefore Mg loss from the serum results continent Mg deficiency and in the other hand along normal serum Mg level, intracellular Mg deficiency can be existed. The serum Mg level is controlled by the kidney, to reach the normal level women need 300 mg, men need 380 mg Mg intake per a day.

The development of Mg deficiency is usually due to dietary alterations. Under certain studies 75% of the population in USA cannot obtain to the advisable Mg intake. The

inadequate alimentation, the low Mg content in fruits and vegetable, the alcohol consumption, and certain drugs (diuretics) usage leads to the development of Mg deficiency. In Hungary we also had a study, which investigated the Mg intake of the population, the average intake in women was 372 mg, in men 441 mg, this is corresponds to the normal amount, but individual alterations cannot be expelled. Significant Mg deficiency can be developed in case of vomiting, diarrhea, hypercalciuria, glucosuria, usage of diuretics, regularly alcohol consumption. Hungry bone syndrome can develop after the operation of hyperparathyreosis. The most symptoms of Mg deficiency are not specific. In the cerebral form the main symptoms are headache, migraine, vertigo, nystagmus, loss of concentration.

Based on a previous studies showing evidence of Mg reduction in patients with migraine, Mg deficiency may play an important role in migraine pathogenesis. Low levels of Mg increase the aggregation of the platelets, therefore serotonin is able to evolve leading to intracerebral arterial vasoconstriction. The increased level of serotonin is responsible the excretion of substance P, which plays a part of the evolution of pain. Besides Mg has a Ca-channel blocking effect, Mg is able to control the influx of Ca into the endothelial and muscle cells, therefore in case of Mg deficiency Ca channels act more active, vasoconstriction develops more easily. Reduced Mg level enhance the sensitivity of the NMDA receptors to glutamate, facilitating the development of cortical spreading depression. The evidence that Mg plays a part in the initiation of primary headache is the observation that in case of migraine or cluster headache administration of 1 g $MgSO_4$ can terminate the symptoms.

The measurement of serum magnesium is widely used to assess total body Mg status, but normal serum Mg concentration also can occur in the presence of tissue Mg depletion with the compensation of by the bone Mg pool. Intracellular Mg content (from leucocytes, lymphocytes, red blood cell, platelets) has been investigated in the hope that it would be a better indicator of Mg status than the serum Mg concentration, but intracellular Mg concentration pools do not seem to correlate with other tissue pools. The most accurate methods to asses Mg status are the Mg load test and muscle or bone biopsies. Mg load test was use in earlier to investigate the Mg deficiency in case of fatty acid malabsorption and protein-calorie malnutrition in elderly. Normally 80 % of the Mg intake can excrete by the kidneys under 48 hours.

In the study reported here, we sought to determine the total body Mg status of patients with migraine by administering an oral Mg load test and comparing the migraineur's serum and urinary Mg concentrations with those obtained from healthy subjects.

4.2. Patients and methods

4.2.1. Subjects

We evaluated 20 patients with migraine (15 women and 5 men; mean age, 37.9 years; age range, 16 to 52 years) and 20 healthy age-matched volunteers (16 women and 4 men; mean age, 39.6 years; age range, 21 to 54 years). The clinical diagnoses of the patients with migraine were based on the headache classification system of the International Headache Society (HIS 1988). Sixteen patients having migraine without aura (IHS 1.1), and 4 patients experiencing migraine with aura (IHS 1.2) were treated. The Mg load test was performed during an attack free period in all patients. Patients and subjects with a history of Mg supplementation within the year prior to the load test or those with special dietary habits were excluded from the study. To reduce the methodological limitations resulting from differences in body weight, we selected subjects who had a normal body mass index and less than 10% variation in body weight from fellow subjects. Neither the controls nor the patients were taking any medication known to interfere with Mg status, none of them have chronic disorder bordering internal medicine. Alcohol intake and heavy physical activity were not allowed during the collection periods.

4.2.2. Magnesium loading and sample collection

The Mg load test was performed on 2 consecutive days. In order to determine the baseline serum Mg levels and the baseline urinary Mg excretions, blood was obtained, in the morning of the first day, followed by a 24-hour urine collection. On the second day, three divided 1000-mg doses of Mg lactate were administered orally to each subject, and a 24-hour urine specimen was collected. To determine the post load serum Mg levels, venous blood was drawn at the end of the second day.

4.2.3. Sample preparation and measurement

The concentration of Mg in serum and urine was measured by a Varian spectrAA-20 atomic absorption spectrophotometer. In our laboratory, the reference ranges for Mg concentration are 0.70 to 1.00 mmol/L for serum, and 2.2 to 5.6 mmol/24 hours for urine.

4.2.4. Statistical analysis

Statistical analysis was performed using Statistica for Windows version 5.1 statistical package (StatSoft, Inc, Tulsa, Okla). Paired *t* test, Pearson correlation, F-test was used.

4.3. Results

1. The mean serum and 24-hour urine Mg concentrations obtained before and after Mg loading are listed in the Table 1.

Table 1. Serum and urine Mg concentrations

	serum Mg concentration mmol/l		urine Mg excretion mmol/24 hour	
	control (n=20)	migraine (n=20)	control (n=20)	migraine (n=20)
Before Mg load	0.81±0.08	0.80±0.04	3.99±1.51	3.18±1.18
After Mg load	0.89±0.11	0.86±0.07	5.9±1.63	4.16±1.33

±Values are means SD.

The baseline serum Mg values were within the reference range in both groups, while the baseline Mg values from the 24-hour urine collection were below normal in four migraineurs and in one control subject.

2. The baseline serum Mg concentrations and urinary excretions increased in all subjects after Mg loading. Although the serum Mg levels were somewhat lower in the patients with migraine than in the controls before and after Mg administration, this difference was not significant. Preload urinary Mg excretion was lower in the patients with migraine than in the normal subjects, but the difference, too, was not significant (p=0.064). After loading, however, the Mg excretion of the patients with migraine was significantly lower than that of the controls (p=0.0007). Within the groups, significant correlations were not found in the comparison of serum Mg concentrations in the 24-hour urine excretion values in either the preload or the postload periods.

4.4. Discussion

It is thought there is possible relationship between Mg deficiency and the development of migraine. In case of Mg deficiency platelet aggregation and therefore the consecutive release of serotonin from platelets may increase, this can provoke arterial vasoconstriction. In the other hand it can enhance the sensitivity of NMDA receptors enlarging the risk of development of CSD.

Previous ictal and interictal studies of patients with migraine have revealed reduced levels of Mg concentrations in serum, saliva, red blood cells, mononuclear cells, lymphocytes, cerebrospinal fluid, and brain. In other investigations, a deficiency of Mg has been less evident or altogether lacking. Measurements of intracellular and ionized Mg concentrations are sensitive methods for demonstrating Mg deficiency, but because there is little evidence for dynamic equilibrium among body tissues, these methods give only limited information about

total body Mg status.. For this reason, we chose the widely accepted Mg load test in our effort to determine whether systemic Mg deficiency exists in patients with migraine.

The baseline serum and urine Mg concentrations recorded in our migraine and control groups did not differ significantly. These results are consistent with previous reports showing normal total serum Mg levels in patients with migraine in both the ictal and interictal states. The 24-hour urine excretion of Mg may be a better indicator of tissue status than the serum Mg concentration, but urinary Mg excretion is highly variable and so cannot be used reliably to assay a given individual's Mg status. After loading, Mg levels in serum and in excreted urine increased significantly in both of our subject groups, simply demonstrating the absorption and bioavailability of orally administered Mg. Urinary Mg excretion did not correlate with serum Mg concentration indicating that renal excretion values reflect the complex interrelations of the different Mg pools. The post load serum Mg concentrations did not differ between our two groups, but the Mg content in the excreted 24-hour urine was significantly lower in the migraine group than in the control group. In short, our patients with migraine retained more Mg than our control subjects, and such retention is considered to reflect systemic Mg deficiency.

There are numerous etiologies for primary and secondary Mg deficiency. Deficiency may be due to reduced dietary intake, smoking, consumption of alcohol, intestinal malabsorption and defective membrane transport, stress, or genetically impaired intracellular regulations. Females have a greater tendency for Mg deficiency than males, presumably nonresponders exhibited significantly higher baseline total Mg levels than responders. In two double-blind, placebo- controlled studies evaluating oral supplementation for migraine prophylaxis, patients receiving Mg experienced reductions in attack frequency and number of days with headache. In the third trial of Mg prophylaxis, no difference in efficacy was observed between the migraine and placebo groups; poor absorption of the Mg salt selected was blamed for the negative result. In conclusion, the oral Mg load test may represent an effective, noninvasive means for detecting systemic Mg deficiency in patients with migraine. It should be noted that this test requires strict subject cooperation and has not been standardized for routine clinical use. Even so, our data add to the growing amount of literature supporting the role of Mg deficiency in the pathogenesis of migraine.

5. Methylprednisolone therapy for short-term prevention of SUNCT syndrome

5.1. Introduction

Trigeminal autonomic cephalalgia (TAC) is a collective term that refers to a group of headaches characterized by episodic or chronic, short-lasting, unilateral head or face pain with accompanying autonomic features. TACs include cluster headache, paroxysmal hemicrania and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT). The pathophysiology of TACs involves activation of trigeminovascular nociceptive pathways with cranial autonomic activation, which is due to central disinhibition of the trigeminal autonomic reflex by the hypothalamus.

Despite the fact that TACs share common pathophysiological pathways, there are dissimilarities among the headache syndromes not only in the basic clinical features (e.g. in SUNCT the duration of pain and autonomic symptoms is the shortest, the incidence of daily attacks is the highest), but also in response to therapy. Most of the current treatment options for TACs are rather empirical than pathophysiology-based, and little is known concerning the mechanism of action of the pharmacological agents used as acute and prophylactic therapy. In cluster headache and in paroxysmal hemicrania there are some accomplished and well-tolerated, therefore recommended, acute and preventive medications. However, in the rare SUNCT syndrome we have only case reports with frequently disappointing therapeutic effectiveness. Abortive therapy of SUNCT is meaningless because of its characteristic short and frequent pain attacks. Intravenous lidocaine has been suggested for short-term prevention, but this treatment requires hospitalization, and complete pain relief was only in a fraction of the treated patients reported. Among all medications attempted in SUNCT, lamotrigine was most effective for long-term prevention, but patients need to be particularly vigilant during the initiation of therapy because of possible skin reactions, which may even progress to Stevens–Johnson syndrome. The risk can be reduced by slow introduction and titration; however, during this period, which might last for a few weeks, the patient has no efficient symptom relief. In cluster headache corticosteroids are very effective in suppressing the headache period and are therefore recommended for short- term prevention. In SUNCT syndrome only a few corticosteroid-treated cases have been reported with partial effectiveness.

During the past few years, only three patients with idiopathic, episodic SUNCT syndrome were referred to our Outpatient Headache Department. All patients had been unsuccessfully treated during their previous headache periods. Based on the success of cluster

headache corticosteroid treatment, we tried methylprednisolone therapy for short-term prevention in all three patients to minimize their disability during the headache period.

5.2. Case histories

5.2.1. Patient 1

A 60-year-old man was examined for frequent headache paroxysms (15–40/day) lasting 30–150 s with few minutes-long refractory periods between the attacks. Although most of his attacks were spontaneous, he could sometimes trigger the headaches with forced and repeated eye closure. The left-sided orbital/supraorbital pain [intensity 10/10 on the visual analogue scale (VAS)] was associated with ipsilateral cranial autonomic symptoms such as conjunctival injection, tearing, eyelid oedema, nasal congestion and rhinorrhoea. The headaches occurred in cluster periods, once or twice every year, lasting for 30–60 days for 13 years. There was no chronic disorder in his medical history and he was not on regular medication. He did not smoke and there was no history of other headaches. Neurological and ophthalmological examinations, routine blood tests and 3T brain magnetic resonance imaging (MRI) studies were normal. Previous treatments with non-steroid anti-inflammatory drugs (NSAIDs; diclofenac, ibuprofen, indomethacin, naproxen), carbamazepine, gabapentin and pregabalin had not proved effective. He took methylprednisolone in a daily dose of 1 mg/kg for 2 weeks, then in reduced dose (16 mg dose reduction/week) for 4 weeks. The therapy had been repeated four times during the last 3 years. The medication was started on the first day of the headache bout in each period, and the steroid therapy lasted for 4–6 weeks. To decrease the possible side-effects of corticosteroid treatment, the histamine H2 receptor antagonist famotidine in a daily dose of 80 mg and potassium chloride in a daily dose of 1000 mg were co-administered with the methylprednisolone therapy. His pain intensity and the number of daily headaches decreased dramatically within 48 h, and then he became attack-free in all treated periods. Treatment-related side-effects did not occur.

5.2.2. Patient 2

A 75-year-old non-smoker man had suffered from repeated headache periods for 11 years. The periods lasted for 20–40 days and had appeared not more than once per year during periods of weather transition in the spring or autumn. He complained of stabbing and burning pain in the left orbital, and periorbital regions along with tearing and conjunctival injection. The intensity of his headaches measured by VAS was 10/10. The duration of pain attacks was 45–120 s and the headaches occurred 20–70 times every day without triggering refractory

periods between the attacks. There was no reported nausea or vomiting, and he could trigger the attacks with speaking, eating and face grimacing. The patient did not have any other type of headache. His medical history consisted of well controlled type II diabetes, hypertension and cardiac atrial fibrillation. Neurological, ophthalmological and otorhinolaryngological examinations were normal; a routine blood test showed only an increased International Normalized Ratio level, which was explained by chronic anticoagulant therapy. 3T brain MRI images demonstrated small signal abnormalities in the hemispheric white matter, but the brainstem was intact and there was no sign of trigeminal nerve vascular or nonvascular compression. Previous medications including NSAIDs (diclofenac, ibuprofen), clomipramine, carbamazepine, gabapentin and pregabalin did not alleviate the symptoms. He was treated with methylprednisolone (1 mg/kg every day) during his last two headache periods. The therapy started on the first day of the attacks in each period, and both the intensity and frequency of the attacks improved within 3 days and then he became pain-free. The corticosteroid treatment was tapered after 2 weeks by 4 mg every day and was finally discontinued within 3 weeks. The remission was maintained during the treatment period and the headaches did not relapse afterward. To decrease the possible side-effects of corticosteroid treatment, the histamineH2 receptor antagonist famotidine at a daily dose of 80 mg and potassium chloride at a daily dose of 1000 mg were co-administered with the methylprednisolone therapy. The dose of his regular oral antidiabetic drug was increased during the treatment period. The patient tolerated the treatments well during both period

5.2.3. Patient 3

A 27-year-old man had reported his first headache period 8 years before his neurological examination. The short-lasting (5–45 s), frequent (up to 100/day), severe (10/10 in intensity by VAS) and unilateral headaches developed in his right temple, eye and upper teeth. There was no refractory period between the attacks. The pain was sharp and stabbing. There was no nausea, light or noise sensitivity. The headaches were associated with ipsilateral conjunctival injection, tearing and nasal congestion. The pain could be triggered by touch of the forehead, temple and chin, as well as by chewing, drinking cold water and brushing of teeth. The headache period occurred twice per year (spring and autumn) and lasted for 2 or 3 weeks. He was a non-smoker and past medical history revealed only Gilbert syndrome. Ear, nose, teeth and throat examinations were negative, and he did not have any pathological neurological signs. Routine laboratory tests showed only a mildly increased bilirubin level, while brain 3T MRI was normal. The patient was not on a daily medication, and previously he had used

different NSAIDs (diclofenac, ibuprofen, indomethacin, nimesulide), carbamazepine and amitriptyline for his headache without any effect. He had taken methylprednisolone at a 1 mg/kg daily dose on the second day of his last headache period and his pain attacks had completely disappeared within 48 h. To decrease the possible side-effects of the corticosteroid treatment, the histamine H2 receptor antagonist famotidine at a daily dose of 80 mg and potassium chloride at a daily dose of 1000 mg were co-administered with the methylprednisolone therapy. After 2 weeks' corticosteroid therapy the daily dose was reduced by 8 mg every day until it was discontinued.

5.3. Discussion

In this study we treated three patients with oral administration of methylprednisolone in daily doses of 1 mg/kg. All patients fulfilled the International Headache Society classification criteria of episodic SUNCT syndrome. The headache bouts were refractory to all previously used medications, including different NSAIDs, antiepileptic and tricyclic antidepressant drugs. We have treated a total of eight SUNCT episodes with oral methylprednisolone in these patients, and the headache periods were completely suppressed in all cases.

Based on previous reports, there is no curative on consistently effective drug treatment for SUNCT syndrome. Therapy of acute attacks is not a useful concept as the attacks are very short in duration. Furthermore, abortive therapy may result in overmedication and toxicity. Therefore, preventive therapy is suggested to suppress attacks and to maintain remission over the expected duration of the headache period. The prophylactic pharmacological therapy works much more effectively in episodic SUNCT than in chronic patients, and success of the treatment depends on the pharmacological agent and its dose. Various classes of medication used in other headache syndromes have been tried for the treatment of SUNCT and have had poor effectiveness. These include NSAIDs (indomethacin, nimesulide), analgesics (paracetamol, opiates), 5-HT agonists (triptans, ergotamine), b-blockers (propranolol, timolol), a-adrenoreceptor agonist (clonidine), tricyclic antidepressants (amitriptyline, nortriptyline, desipramin), calcium channel blockers (nifedipine, flunarizine, diltiazem), antiepileptic drugs (phenytoin, valproic acid, clonazepam), lithium and baclofen.

In short-term prevention intravenous and subcutaneous lidocaine provided the patients some pain relief up to total pain abolition. Although cardiac adverse events did not occur, hospitalization and cardiac monitoring were necessary. Lamotrigine given 125–400 mg/day is the first-line recommendation for long-term prevention, and has a good effect in achieving

complete remission or attack frequency reduction in most SUNCT patients. The main problem with lamotrigine is that the dose titration is very slow because of the possible skin reactions. In second-line prevention topiramate can be effective at doses of up to 300 mg/day as > 50% of patients had a good response to it. However, topiramate may cause severe side-effects and its administrationis not suggested in patients with a history of renal stones, glaucoma, depression, or low body weight. Gabapentin can be effective also as a second-line agent in SUNCT in doses ranging from 800 to 3600 mg daily. Interestingly, this drug was more effective in patients with shortlasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) (60%) than in SUNCT (45%) (12). Carbamazepine has also been reported as having a good effect in SUNCT at doses of up to 900 mg/day, especially when used in combination with steroids or topiramate.

Although there is no evidence-based recommendation for corticosteroid use in SUNCT syndrome, a few case reports are known where patients were treated by prednisone, prednisolone or methylprednisolone with moderate to excellent therapeutic response. Blockade of the greater occipital nerve with steroids and local anaesthetics were also tried in certain cases of SUNCT and were found to have moderate or good efficacy, but this treatment worked better in cluster headache. Conversely, corticosteroids are advised in cluster headache for short-term prevention; however, randomized, placebo-controlled trials are unavailable. The 21-day long oral prednisolone therapy is started with 1 mg/kg (maximum 60– 100 mg) once daily for 5 days; thereafter the dose is decreased by 10 mg every day or every 3 days. With this method the risks of long-term steroid use (diabetes, hypertension) can be minimized. The mechanism of methylprednisolone action is unclear, although it is probably based on the anti-inflammatory effect of the drug. Methylprednisolone works via the glucocorticoid receptor by suppressing the expression of proinflammatory cytokines and also affecting the production of inflammatory mediators. It is known that in cluster headache the pain is a result of trigeminal nerve activation causing the release of vasodilative neurotransmitters such as substance P, serotonin (5-HT), nitric oxide, endothelins, calcitonin generelated peptide (CGRP), vasoactive intestinal peptide (VIP) and interleukin (IL)-1, which is a cytokine acting in perivascular inflammation. It has been assumed that corticosteroids develop their influence by moderating the level of certain neurotransmitters (CGRP, VIP, histamine, 5-HT) and vasoactive inflammatory agents (IL-1), thereby decreasing the perivascular sterile inflammation.

In conclusion, orally administered methylprednisolone therapy proved effective in rapid and complete headache resolution in patients with episodic SUNCT syndrome.

Symptoms did not relapse at the end of the expected headache cycle when the therapy was discontinued. Furthermore, intolerable side-effects were not manifested during the treatment periods. In case of longer headache periods, corticosteroid therapy would give time for introduction and titration of other preventive medication.

6. Summary and novel findings

In the thesis we investigated three different topics related to the primary headaches.

In the first part those risk factors were analyzed in migraine patients, which can lead to the development of migraine related brain white matters hyperintensities. The data of 186 migraine patient were studied including medical history, comorbidity, smoking habit, routine laboratory test, and the characteristics of their headache. The incidence of brain WMH in case of migraine patients was influenced by the duration of headache and the attack frequency. Also increased WMH can be observed in migraine when elevated serum homocysteine, cholesterol, LDL and uric acid are present.

In the second part of thesis we studied the possible relationship between migraine and Mg deficiency. An oral Mg load test was administer to detect the total body Mg deficiency in case of migraine patients. We found total body Mg deficiency in migraineurs. It can be propounded that the supplementation of Mg may prevent the development of migraine.

In the third part, three SUNCT patients were investigated. The time-tested lamotrigine therapy acts only as long-term prevention therapy, because we have taper the dose very slowly by the possible serious skin side reaction. Analogously to the cluster headache we tried to treat the SUNCT periods with steroid medication. In all cases the steroid administration were successful, after three days of treatment the headache terminated, therefore we can advise the steroid to short-term prevention therapy in SUNCT headache.